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TITLE OF INVENTION
HETEROCYCLIC COMPOUNDS AND THEIR USE AS ANTICANCER AGENTS

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Respectfully submitted,

SIGNATURE [signature] Date: July 9, 2003

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HETEROCYCLIC COMPOUNDS AND THEIR USE AS ANTICANCER AGENTS

FIELD OF THE INVENTION

The present invention relates to heterocyclic compounds and their derivatives that have anticancer activity, pharmaceutical compositions that contain the compounds, methods for making the compounds, and methods of treating cancer in mammals by administering a therapeutically effective amount of the compounds to said mammals.

BACKGROUND OF THE INVENTION

Malignant tumors, characterized by abnormal proliferation of neoplastic cells, are one of the most common diseases worldwide, and the subset of human cancer types amenable to curative treatment is rather small. Although there is tremendous progress in understanding the molecular events that lead to malignancy, there is still a high demand for the development of clinically innovative drugs that can effectively inhibit proliferation of cancer cells and cure human cancer.

Taxol is the most promising antitumor agent developed in the past three decades, effective for treatment of ovarian and breast cancers, with a worldwide sale of USD 1.5 billion in 2002. As taxol halts proliferation of cancer cells by acting on microtubules, its success as a chemotherapeutic agent brought the focus back to the potential of microtubules as a potential target.

Microtubules are elements of the cell cytoskeleton that play a key role in cell division, shape and motility, as well as intracellular transport. Microtubules are highly dynamic structures formed by polymers of tubulin. During cell division microtubules disassemble into soluble tubulin dimers, prior to their reassembly and formation of the mitotic spindle, a structure that provides segregation of replicated chromosomes to daughter cells. For proper cell division to occur, it is essential that microtubules are able to polymerize and depolymerize. Microtubules in the mitotic spindle are more dynamic than those in non-dividing cells, and thus can be targeted

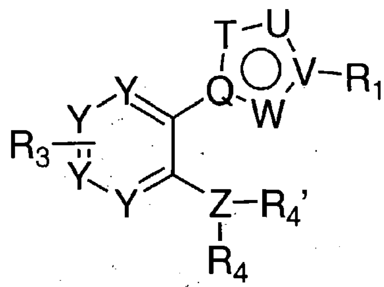
by agents that affect tubulin dynamics. By altering microtubule polymerization/ depolymerization these agents affect mitotic spindle function, arrest dividing cells in the G2/M phase of the cell cycle, and ultimately lead to apoptotic cell death. As neoplastic cells have high proliferation rates, they can be targeted by these antimitotic agents. Compounds that bind to tubulin, interfere with microtubule dynamics and inhibit proliferation of cancer cells and are indeed some of the most effective cancer therapeutic agents in use.

However, clinically available compounds such as Taxol or Vincristine are facing severe disadvantages, namely, (1) high toxicity, (2) marginal bioavailability and poor solubility, (3) complex synthesis or isolation procedures, and (4) development of drug resistance in patients. Therefore, synthetic low molecular weight compounds with oral bioavailability and high therapeutic index for first and second line therapy are urgently needed.

Because of their clinical potential, several synthetic molecules that bind to tubulin are currently being evaluated in preclinical or early clinical stage. Most notably, WO 01/22954, assigned to Asta Medica, discloses indole-3-glyoxylamide derivatives with antitumor activity. One compound, D-24851, has been shown to exert curative antitumoral activity *in vivo*, shows efficacy toward MDR cells and lacks neurotoxicity (Cancer Research 61, 392, 2001). DE 10020852, assigned to Asta Medica, discloses 1H-indol-2-yl aryl ketones and related compounds as antitumor agents. Specifically, D64131 has been shown to be orally active, efficacious in xenograft models and showed no signs of toxicity (Cancer Research 62, 3113, 2002). ZA 2000000419, assigned to Abbott, discloses oxadiazoline derivatives as antiproliferative agents. A-204197 has shown to be effective against Taxol resistant cell lines. (Cancer Research 61, 5480, 2001). U.S. patent 6,521,658, also assigned to Abbott, discloses certain sulfonamides as cell proliferation inhibitors. WO 02/39958, assigned to Tularik, discloses combination therapy using pentafluorobenzenesulfonamides and antineoplastic agents. Compounds that have anticancer activity either mainly or partially due to their effects on microtubules are of great interest as novel therapeutics.

SUMMARY OF THE INVENTION

In one aspect, the invention relates to heteroarylaminophenylketone derivatives, which are kinase inhibitors, that have the following structural formula I:



(I)

or pharmaceutically acceptable salts, stereoisomers, hydrates or pro-drugs thereof,

wherein Y = N or C-R,

Z = O, N, C, S, C=O, S=O, O=S=O,

Q, T, U, V and W can be independently O, N, N-R, C, C-R or S,

R_1, R_3, R_4 and $R_{4'}$ are independently:

1) lower alkyl, optionally substituted with one or more substituents selected from R_2,

2) lower alkenyl, optionally substituted with one or more substituents selected from R_2,

3) aralkyl, optionally substituted with one or more substituents selected from R_2,

4) lower alkynyl, optionally substituted with one or more substituents selected from R_2,

5) aryl or heteroaryl, optionally substituted with one or more substituents selected from R_2,

6) non-aromatic heterocyclic group, optionally substituted with one or more substituents selected from R_2,

7) halogen,

8) nitro,

9) cyano,

10) trifluoromethyl,

11) a group of the formula -CO2R, -OR, -SR, -S(=O)R, -SO2R, -NH2, -NHR, -NRR, where R is independently selected from H, lower alkyl, aralkyl, aryl, and heteroaryl,

each R_2 is independently selected from:

1) halogen,

2) lower alkyl, which may be optionally substituted with one or more halogen, hydroxy, lower alkoxy,

3) lower alkenyl, which may be optionally substituted with one or more halogen, hydroxy, lower alkoxy,

4) nitro,

5) cyano,

6) a group of the formula -CO2R, -OR, -SR, -SO2R, -NH2, -NHR, -NRR,

or R_2 can occupy two adjacent positions to form a fused 5- or 6-membered carbocyclic or heterocyclic ring, wherein heterocyclic ring may contain from 1 to 2 heteroatoms selected from N, O or S, and

each R is independently selected from hydrogen, halogen, lower alkyl, aralkyl, aryl, and heteroaryl,

In a second aspect, the invention relates to a pharmaceutical composition comprising a pharmaceutical acceptable carrier or diluent and a compound represented by structural formula (**I**). Preferably, a pharmaceutical composition comprises an effective amount of the compound. The pharmaceutical compositions can be used in therapy, for example, to treat a subject with cancer.

Another embodiment of the present invention is the use of a compound represented by structural formula (**I**) for the manufacture of a medicament for treatment of a subject with cancer. The medicament comprises an effective amount of the compound.

Another embodiment is the method of treating a subject with cancer. The method comprises administering to the subject an effective amount of a compound represented by structural formula (**I**).

The invention further relates to a method of making the compounds of formula I.

The present invention will now be described in detail for specific preferred embodiments of the invention. These embodiments are intended only as illustrative examples and the invention is not intended to be limited thereto.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides compounds of formula I as described above.

The term "lower alkyl" as used herein refers to a saturated hydrocarbon derived radical containing from 1 to 6 carbon atoms. The lower alkyl group may be straight, branched or cyclic. Straight or branched lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl and t-butyl, and the like. Cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "lower alkenyl" as used herein refers to a non-aromatic hydrocarbon radical, straight, branched or cyclic, containing from 2 to 6 carbon atoms and at least one carbon to carbon double bond. Lower alkenyl groups include ethenyl, propenyl, butenyl cyclohexenyl, and the like.

The term "lower alkynyl" as used herein refers to a hydrocarbon radical that is straight, or branched, containing from 2 to 6 carbon atoms and at least one carbon to carbon triple bond. Lower alkynyl groups include ethynyl, propynyl and butynyl, and the like.

The term "aralkyl" as used herein contemplates a lower alkyl group which has as a substituent an aryl group.

The term "aryl group" refers to carbocyclic aromatic groups such as phenyl, naphthyl, and anthracyl, and heteroaryl groups such as imidazolyl, isoimidazolyl, thienyl, furanyl, pyridyl, pyrimidyl, pyranyl, pyrazolyl, pyrrolyl, pyrazinyl, thiazoyl, isothiazolyl, oxazolyl, isoxazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, and tetrazolyl. Aryl groups also include the fused polycyclic aromatic ring systems in which a carbocyclic aromatic ring or heteroaryl ring is fused to one or more other heterocyclic rings. Examples are benzothienyl, benzofuranyl, indolyl, quinolinyl, benzothiazolyl, benzoisothiazolyl, benzoxazolyl, benzoisoxazolyl, benzimidazolyl, quinolinyl, isoquinolinyl, isoindolyl, indolizinyl and indolinyl.

The term "non-aromatic heterocyclic groups" refers to non-aromatic carbocyclic rings, which included one or more heterotoms such as nitrogen, oxygen, or sulfur in the ring. The ring can be three to eight membered. Examples include aziridinyl, oxazolinyl, thiazolinyl, oxazolidinyl, thiazolidinyl, tertrahydrofuranyl, tetrahydrothiophenyl, morpholino, thiomorpholino, pyrrolidinyl, piperidinyl, piperazinyl, thiazolidinyl and homopiperazinyl.

The term "alkoxy" as used herein refers to a substituent with an alkyl group in either a straight-chained or branched configuration, and may include a double or a triple bond, which is attached via an oxygen atom. The alkyl portion may be substituted or unsubstituted. Substituents on the alkyl group may include for example, a phenyl ring, in which the alkoxy may be for example, a benzyloxy group. Examples of alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy allyloxy, propargyloxy, vinyloxy, and the like.

The term "halo" or "halogen" as used herein is intended to include the halogen atoms fluorine, chlorine, bromine and iodine.

When one or more chiral centers are present in the compounds of the present invention, the individual isomers and mixtures thereof (e.g., racemates, etc.) are intended to be encompassed by the formulae depicted herein.

As used herein the terms "pharmaceutically acceptable salts" and "hydrates" refer to those salts and hydrated forms of the compound that would be apparent to those in the art, *i.e.*, those which favorably affect the physical or pharmacokinetic properties of the compound, such as solubility, palatability, absorption, distribution, metabolism and excretion. Other factors, more practical in nature, which those skilled in the art may take into account in the selection include the cost of the raw materials, ease of crystallization, yield, stability, solubility, hygroscopicity and flowability of the resulting bulk drug.

When a compound of the present invention is present as a salt or hydrate that is non-pharmaceutically acceptable, that compound can be converted in certain circumstances to a salt or hydrate form that is pharmaceutically acceptable in accordance with the present invention.

When the compound is negatively charged, it is balanced by a counterion, such as, an alkali metal cation such as sodium or potassium. Other suitable counterions include calcium, magnesium, zinc, ammonium, or alkylammonium cations, such as tetramethylammonium, tetrabutylammonium, choline, triethylhydroammonium, meglumine, triethanol-hydroammonium, and the like. An appropriate number of counterions are associated with the molecule to maintain overall charge neutrality. Likewise, when the compound is positively charged, *e.g.*, protonated, an appropriate number of negatively charged counterions are present to maintain overall charge neutrality. These pharmaceutically acceptable salts are within the scope of the present invention.

Also included in the present invention are pharmaceutically acceptable salts of the compound described within. Compounds disclosed herein which possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly can react with any of a number of organic or inorganic bases, and organic or inorganic acids, to form a salt. Acids commonly employed to form acid addition salts from compounds with basic groups are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as para-toluenesulfonic acid, methanesulfonic acid, oxalic acid, para-bromophenyl-sulfonic acid, carbonic acid, succinic acid, citric acid, benzoic

acid, acetic acid, and the like. Examples of such salts include the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propiolate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propionate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, gamma-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphalene-1-sulfonate, naphthalene-2-sulfonate, mandelate, and the like.

If the compound has an acidic proton, a salt may be form by the addition of base to form a pharmaceutically acceptable base addition salt. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth.

The basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

The presence of pharmaceutically acceptable salts within the scope of the present compounds is not intended to limit the compounds of the present invention to those that are synthetically prepared. The compounds of the present invention also include compounds that are converted within the body and prodrugs. "Pro-drug" means a form of the compounds of the present invention suitable for administration to a patient without undue toxicity, irritation, allergic response, and the like, and effective for their intended use. A pro-drug is transformed *in vivo* to yield the parent compound of the formula I herein, for example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery*

Systems Vol. 14 of the A. C. S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987.

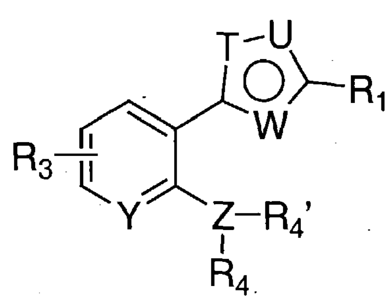
The compounds of the present invention, may have asymmetric centers and occur as racemates, mixtures or enantiomers and as individual enantiomers with all isomeric forms being included in the present invention.

The disclosed compounds can be used to treat subjects with cancer, including multi-drug resistant cancers. A cancer is resistant to a drug when it resumes a normal rate of tumor growth while undergoing treatment with the drug after the tumor had initially responded to the drug. The term "multi-drug resistant cancer" refers to cancer that is resistant to two or more drugs, typically five or more.

The disclosed compound can be co-administered with other anticancer agents such as Taxol, Vincristine, Adriamycin, Etoposide, Doxorubicin, Dactinomycin, Mitomycin C, Bleomycin, Vinblastine, Cisplatin and the like. The method can also be carried in combination with other cancer treatments such as surgery, radiation, and the like.

A "subject" is a mammal, preferably a human, but can also be an animal in need of veterinary treatment.

In an preferred embodiment, the compound of the present invention is represented by structural formula II:



(II)

wherein Y = N or C-R,

Z = O, N, C, S, C=O, S=O, O=S=O,

T, U, and W can be independently O, N, N-R, C, C-R or S,

R_1, R_3, R_4 and $R_{4'}$ are independently:

1) lower alkyl, optionally substituted with one or more substituents selected from R_2,

2) lower alkenyl, optionally substituted with one or more substituents selected from R_2,

5) aralkyl, optionally substituted with one or more substituents selected from R_2,

6) lower alkynyl, optionally substituted with one or more substituents selected from R_2,

5) aryl or heteroaryl, optionally substituted with one or more substituents selected from R_2,

6) non-aromatic heterocyclic group, optionally substituted with one or more substituents selected from R_2,

7) halogen,

8) nitro,

11) cyano,

12) trifluoromethyl,

11) a group of the formula -CO2R, -OR, -SR, -S(=O)R, -SO2R, -NH2, -NHR, -NRR, where R is independently selected from H, lower alkyl, aralkyl, aryl, and heteroaryl,

each R_2 is independently selected from:

1) halogen,

2) lower alkyl, which may be optionally substituted with one or more halogen, hydroxy, lower alkoxy,

3) lower alkenyl, which may be optionally substituted with one or more halogen, hydroxy, lower alkoxy,

4) nitro,

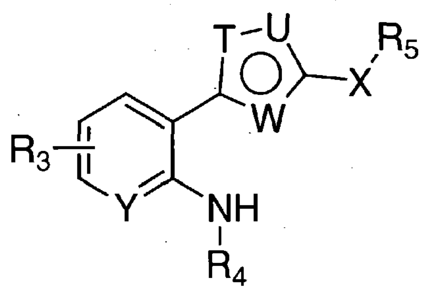
5) cyano,

6) a group of the formula -CO2R, -OR, -SR, -SO2R, -NH2, -NHR, -NRR,

or R_2 can occupy two adjacent positions to form a fused 5- or 6-membered carbocyclic or heterocyclic ring, wherein heterocyclic ring may contain from 1 to 2 heteroatoms selected from N, O or S, and

each R is independently selected from hydrogen, halogen, lower alkyl, aralkyl, aryl, and heteroaryl,

In a more preferred embodiment, the compound of the present invention is represented by structural formula III:



(III)

wherein Y = N or C-R,

X = O, N, CH2, S, C=O, S=O, O=S=O,

T, U and W can be independently O, N, N-R, C, C-R or S,

R_3, R_4 and R_5 are independently:

1) lower alkyl, optionally substituted with one or more substituents selected from R_2,

2) lower alkenyl, optionally substituted with one or more substituents selected from R_2,

7) aralkyl, optionally substituted with one or more substituents selected from R_2,

8) lower alkynyl, optionally substituted with one or more substituents selected from R_2,

5) aryl or heteroaryl, optionally substituted with one or more substituents selected from R_2,

6) non-aromatic heterocyclic group, optionally substituted with one or more substituents selected from R_2,

7) halogen,

8) nitro,

13) cyano,

14) trifluoromethyl,

11) a group of the formula -CO2R, -OR, -SR, -S(=O)R, -SO2R, -NH2, -NHR, -NRR, where R is independently selected from H, lower alkyl, aralkyl, aryl, and heteroaryl,

each R_2 is independently selected from:

1) halogen,

2) lower alkyl, which may be optionally substituted with one or more halogen, hydroxy, lower alkoxy,

3) lower alkenyl, which may be optionally substituted with one or more halogen, hydroxy, lower alkoxy,

4) nitro,

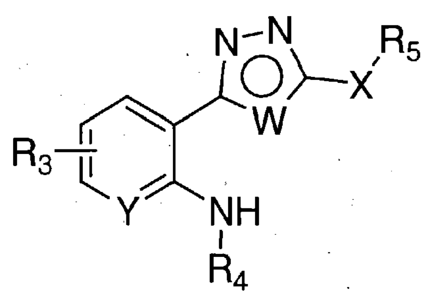
5) cyano,

6) a group of the formula -CO2R, -OR, -SR, -SO2R, -NH2, -NHR, -NRR,

or R_2 can occupy two adjacent positions to form a fused 5- or 6-membered carbocyclic or heterocyclic ring, wherein heterocyclic ring may contain from 1 to 2 heteroatoms selected from N, O or S, and

each R is independently selected from hydrogen, halogen, lower alkyl, aralkyl, aryl, and heteroaryl,

In a even more preferred embodiment, the compound of the present invention is represented by structural formula IV:



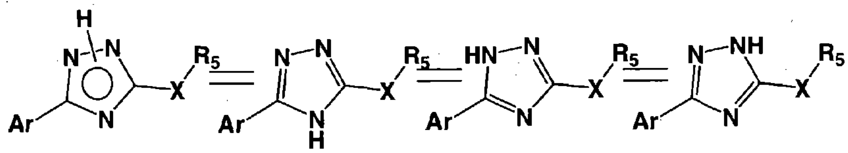
(IV)

wherein Y = N or C-R,

X = O, NH, CH2, S, C=O, S=O, O=S=O,

W = N, NH, NR, O, S

An embodiment of formula (**IV**) is that when W = N or NH, the resulting triazole will compose one or more of the following tautomers:



R_3, R_4 and R_5 are independently:

1) lower alkyl, optionally substituted with one or more substituents selected from R_2,

2) lower alkenyl, optionally substituted with one or more substituents selected from R_2,

9) aralkyl, optionally substituted with one or more substituents selected from R_2,

10) lower alkynyl, optionally substituted with one or more substituents selected from R_2,

5) aryl or heteroaryl, optionally substituted with one or more substituents selected from R_2,

6) non-aromatic heterocyclic group, optionally substituted with one or more substituents selected from R_2,

7) halogen,

8) nitro,

15) cyano,

16) trifluoromethyl,

11) a group of the formula -CO2R, -OR, -SR, -S(=O)R, -SO2R, -NH2, -NHR, -NRR, where R is independently selected from H, lower alkyl, aralkyl, aryl, and heteroaryl,

each R_2 is independently selected from:

1) halogen,

2) lower alkyl, which may be optionally substituted with one or more halogen, hydroxy, lower alkoxy,

3) lower alkenyl, which may be optionally substituted with one or more halogen, hydroxy, lower alkoxy,

4) nitro,

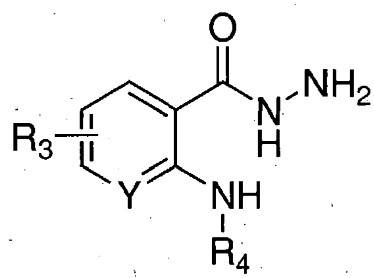
5) cyano,

6) a group of the formula -CO2R, -OR, -SR, -SO2R, -NH2, -NHR, -NRR,

or R_2 can occupy two adjacent positions to form a fused 5- or 6-membered carbocyclic or heterocyclic ring, wherein heterocyclic ring may contain from 1 to 2 heteroatoms selected from N, O or S, and

each R is independently selected from hydrogen, halogen, lower alkyl, aralkyl, aryl, and heteroaryl,

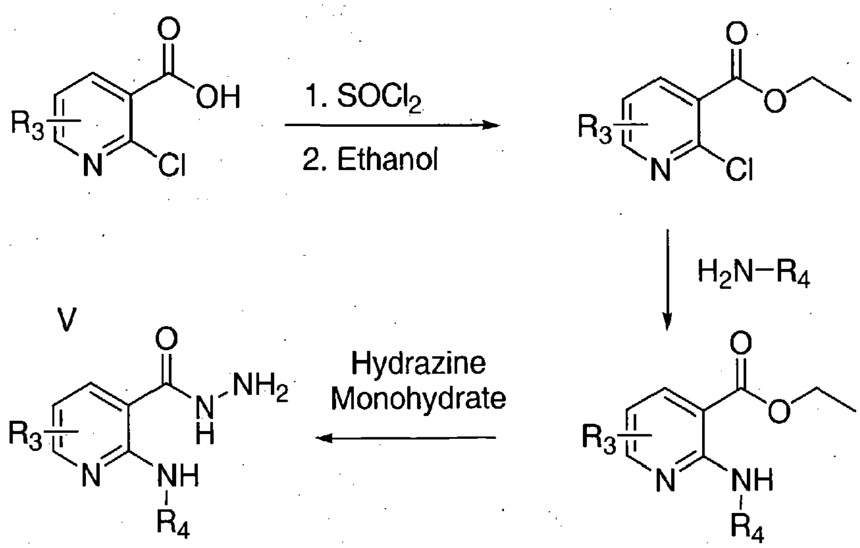
Another embodiment is a method of preparing an intermediate in the synthesis of the compound represented by formula IV. Formula V represents the intermediate:



(V)

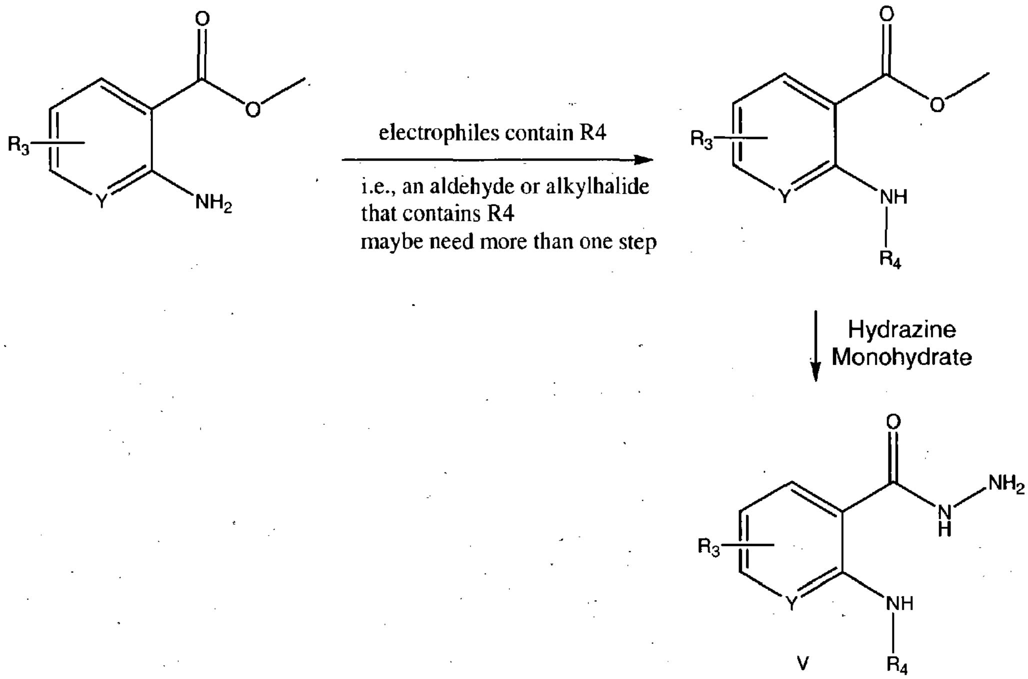
One method of preparing intermediate V is shown in scheme 1:

Scheme I



Another method of making V is shown in scheme 2:

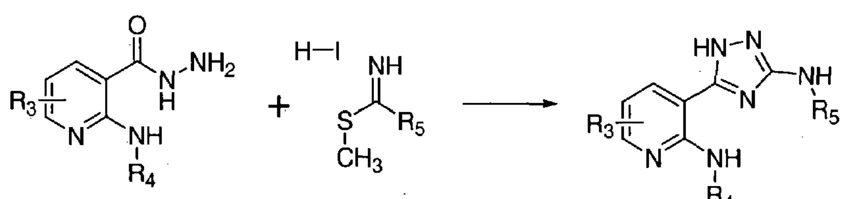
Scheme 2



The invention further relates to a method for making the compounds of formulas IV.

One method of preparing compound of formula IV where W = NH or N and X = NH is shown in scheme 3:

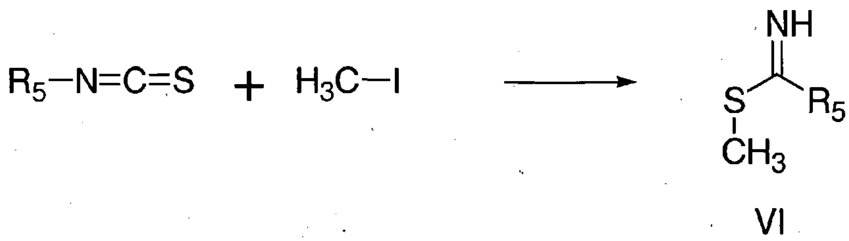
Scheme 3



V VI

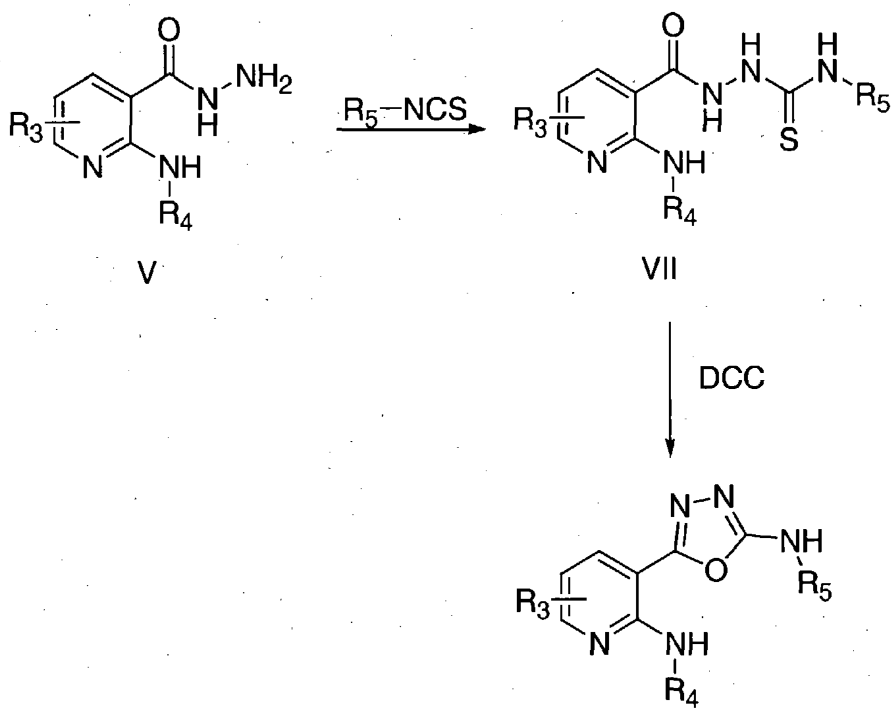
where intermediate VI can be prepared according to scheme 4:

Scheme 4



One method of preparing compound of formula IV where W = O and X = NH is shown in scheme 5:

Scheme 5



Moreover, the compounds of formula I may be used for *in vivo* and *in vitro* investigative, diagnostic, or prophylactic methods, which are well known in the art.

In the methods of the present invention, a therapeutically effective amount of one or more of the Formula I compounds is administered to a mammal in need. The

term "administering" as used herein means delivering the compounds of the present invention to a mammal by any method that may achieve the result sought. They may be administered, for example, orally, parenterally (intravenously or intramuscularly), topically, transdermally or by inhalation. The term "mammal" as used herein is intended to include, but is not limited to, humans, laboratory animals, domestic pets and farm animals. "Therapeutically effective amount" means an amount of compound of the present invention that when administered to a mammal is effective in producing the desired therapeutic effect, such as inhibiting kinase activity.

Another aspect of the present invention relates to pharmaceutical compositions, which include at least one compound of the present invention as described herein (that is, a compound of Formula I) or a pharmaceutically acceptable salt, hydrate or pro-drug thereof, in combination with a pharmaceutically acceptable carrier.

The compounds of the present invention may be employed in solid or liquid form including for example, powder or crystalline form, in solution or in suspension. They may be administered in numerous different ways, such as orally, parenterally (intravenously or intramuscularly), topically, transdermally or by inhalation. The choice of carrier and the content of active compound in the carrier are generally determined in accordance with the solubility and chemical properties of the desired product, the particular mode of administration and the provisions to be observed in pharmaceutical practice. Thus, the carrier employed may be, for example, either a solid or liquid.

One method of administering a solid dosage form is to form solid compositions for rectal administration, which include suppositories formulated in accordance with known methods and containing at least one compound of the present invention. Examples of solid carriers include lactose, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like.

Examples of liquid carriers include syrup, peanut oil, olive oil, water and the like. For parenteral administration, emulsions, suspensions or solutions of the compounds according to the invention in vegetable oil, for example sesame oil,

groundnut oil or olive oil, or aqueous-organic solutions such as water and propylene glycol, injectable organic esters such as ethyl oleate, as well as sterile aqueous solutions of the pharmaceutically acceptable salts, are used. Injectable forms must be fluid to the extent they can be easily syringed, and proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prolonged absorption of the injectable compositions can be brought about by use of agents delaying absorption, for example, aluminum monostearate and gelatin.

The solutions of the salts of the products according to the invention are especially useful for administration by intramuscular or subcutaneous injection. Solutions of the active compound as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropyl-cellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. The aqueous solutions, also including solutions of the salts in pure distilled water, may be used for intravenous administration with the proviso that their pH is suitably adjusted, that they are judiciously buffered and rendered isotonic with a sufficient quantity of glucose or sodium chloride and that they are sterilized by heating, irradiation, microfiltration, and/or by various antibacterial and antifungal agents, for example, Xparabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like.

Examples of injectable dosage forms include sterile injectable liquids, *e.g.*, solutions, emulsions and suspensions. Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation may include vacuum drying and a freeze-dry technique that yields a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

Examples of injectable solids include powders that are reconstituted, dissolved or suspended in a liquid prior to injection. In injectable compositions, the carrier typically includes sterile water, saline or another injectable liquid, *e.g.*, peanut oil for intramuscular injections. Also, various buffering agents, preservatives and the like can be included within the compositions of the present invention.

For oral administration, the active compound may be administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet, or may be incorporated with excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Examples of oral solid dosage forms include tablets, capsules, troches, lozenges and the like. Examples of oral liquid dosage forms include solutions, suspensions, syrups, emulsions, soft gelatin capsules and the like. Carriers for oral use (solid or liquid) may include time delay materials known in the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax. To prepare a capsule, it may be advantageous to use lactose and liquid carrier, such as high molecular weight polyethylene glycols.

Topical administration, in the form of gels (water or alcohol based), creams or ointments, for example, containing compounds of the invention may be used. Topical applications may be formulated in carriers such as hydrophobic or hydrophilic bases to form ointments, creams, lotions, in aqueous, oleaginous or alcoholic liquids to form paints or in dry diluents to form powders. Such topical formulations can be used for example, to treat ocular diseases as well as inflammatory diseases such as rheumatoid arthritis, psoriasis, contact dermatitis, delayed hypersensitivity reactions and the like.

Compounds of the invention may be also incorporated in a gel or matrix base for application in a patch, which would allow a controlled release of compound through transdermal barrier.

For administration by inhalation, compounds of the invention may be dissolved or suspended in a suitable carrier for use in a nebulizer or a suspension or

solution aerosol, or may be absorbed or adsorbed onto a suitable solid carrier for use in a dry powder inhaler.

Compositions according to the invention may also be formulated in a manner that resists rapid clearance from the vascular (arterial or venous) wall by convection and/or diffusion, thereby increasing the residence time of the viral particles at the desired site of action. A periadventitial depot comprising a compound according to the invention may be used for sustained release. One such useful depot for administering a compound according to the invention may be a copolymer matrix, such as ethylene-vinyl acetate, or a polyvinyl alcohol gel surrounded by a Silastic shell. Alternatively, a compound according to the invention may be delivered locally from a silicone polymer implanted in the adventitia.

An alternative approach for minimizing washout of a compound according to the invention during percutaneous, transvascular delivery comprises the use of nondiffusible, drug-eluting microparticles. The microparticles may be included a variety of synthetic polymers, such as polylactide for example, or natural substances, including proteins or polysaccharides. Such microparticles enable strategic manipulation of variables including total dose of drug and kinetics of its release. Microparticles can be injected efficiently into the arterial or venous wall through a porous balloon catheter or a balloon over stent, and are retained in the vascular wall and the periadventitial tissue for at least about two weeks. Formulations and methodologies for local, intravascular site-specific delivery of therapeutic agents are discussed in Reissen et al. (J. Am. Coll. Cardiol. 1994; 23: 1234-1244).

A composition according to the invention may also comprise a hydrogel which is prepared from any biocompatible or non-cytotoxic (homo or hetero) polymer, such as a hydrophilic polyacrylic acid polymer that can act as a drug absorbing sponge. Such polymers have been described, for example, in application WO93/08845. Certain of them, such as, in particular, those obtained from ethylene and/or propylene oxide are commercially available.

Another embodiment of the invention provides for a compound according to the invention to be administered by means of perfusion balloons. These perfusion

balloons, which make it possible to maintain a blood flow and thus to decrease the risks of ischaemia of the myocardium, on inflation of the balloon, also enable the compound to be delivered locally at normal pressure for a relatively long time, more than twenty minutes, which may be necessary for its optimal action.

Alternatively, a channeled balloon catheter (such as "channelled balloon angioplasty catheter", Mansfield Medical, Boston Scientific Corp., Watertown, Mass.) may be used. This catheter includes a conventional balloon covered with a layer of 24 perforated channels that are perfused via an independent lumen through an additional infusion orifice. Various types of balloon catheters, such as double balloon, porous balloon, microporous balloon, channel balloon, balloon over stent and hydrogel catheters, all of which may be used to practice the invention, are disclosed in Reissen et al. (1994).

Another aspect of the present invention relates to a pharmaceutical composition including a compound according to the invention and poloxamer, such as Poloxamer 407, which is a non-toxic, biocompatible polyol, commercially available (*e.g.*, from BASF, Parsippany, N.J.). A poloxamer impregnated with a compound according to the invention may be deposited for example, directly on the surface of the tissue to be treated, for example during a surgical intervention. Poloxamer possesses essentially the same advantages as hydrogel while having a lower viscosity. The use of a channel balloon catheter with a poloxamer impregnated with a compound according to the invention may be advantageous in that it may keep the balloon inflated for a longer period of time, while retaining the properties of facilitated sliding, and of site-specificity of the poloxamer.

The composition may also be administered to a patient via a stent device. In this embodiment, the composition is a polymeric material in which the compound of the invention is incorporated, which composition is applied to at least one surface of the stent device.

Polymeric materials suitable for incorporating the compound of the invention include polymers having relatively low processing temperatures such as polycaprolactone, poly(ethylene-co-vinyl acetate) or poly(vinyl acetate or silicone

gum rubber and polymers having similar relatively low processing temperatures. Other suitable polymers include non-degradable polymers capable of carrying and delivering therapeutic drugs such as latexes, urethanes, polysiloxanes, styrene-ethylene/butylene-styrene block copolymers (SEBS) and biodegradable, bioabsorbable polymers capable of carrying and delivering therapeutic drugs, such as poly-DL-lactic acid (DL-PLA), and poly-L-lactic acid (L-PLA), polyorthoesters, polyiminocarbonates, aliphatic polycarbonates, and polyphosphazenes.

In addition to the active compound and the pharmaceutically acceptable carrier, the compositions of the present invention optionally contain one or more excipients that are conventional in the art. For example, excipients such as lactose, sodium citrate, calcium carbonate, dicalcium phosphate and disintegrating agents such as starch, alginic acids and certain complex silica gels combined with lubricants such as magnesium stearate, sodium lauryl sulfate and talc may be used for preparing tablets, troches, pills, capsules and the like.

Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. When aqueous suspensions are used they may contain emulsifying agents or agents which facilitate suspension. Diluents such as sucrose, ethanol, polyols such as polyethylene glycol, propylene glycol and glycerol, and chloroform or mixtures thereof may also be used. In addition, the active compound may be incorporated into sustained-release preparations and formulations.

The percentage of active ingredient in the compositions of the invention may be varied. Several unit dosage forms may be administered at about the same time. A suitable dose employed may be determined by a physician or qualified medical professional, and depends upon various factors including the desired therapeutic effect, the nature of the illness being treated, the route of administration, the duration of the treatment, and the condition of the patient, such as age, weight, general state of health and other characteristics, which can influence the efficacy of the compound according to the invention. In adults, doses are generally from about 0.001 to about 50, preferably about 0.001 to about 5, mg/kg body weight per day by inhalation; from about 0.01 to about 100, preferably 0.1 to 70, more preferably 0.5 to 10, mg/kg body

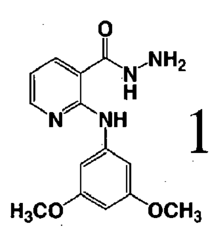
weight per day by oral administration; from about 0.1 to about 150 mg applied externally; and from about 0.001 to about 10, preferably 0.01 to 10, mg/kg body weight per day by intravenous or intramuscular administration.

The compounds and compositions according to the invention may be administered as frequently as necessary as determined by a skilled practitioner in order to obtain the desired therapeutic effect. Some patients may respond rapidly to a higher or lower dose and may find much weaker maintenance doses adequate. For other patients, it may be necessary to have long-term treatments at the rate of 1 to 4 doses per day, in accordance with the physiological requirements of each particular patient. Generally, the active product may be administered orally 1 to 4 times per day. For other patients, it may be necessary to prescribe not more than one or two doses per day.

The compounds of the present invention may also be formulated for use in conjunction with other therapeutically active compounds or in connection with the application of therapeutic techniques to address pharmacological conditions, which may be ameliorated through the application of a compound according to the present invention.

EXAMPLES

Example 1: Synthesis of (3,5-Dimethoxy-phenyl)-{3-[5-(3,5-dimethoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (compound 1)



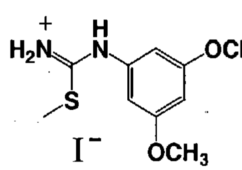
1a

2-(3,5-dimethoxyphenylamino)nicotinic acid hydrazide (1a): 2-Chloropyridine-3-carboxylic acid (25g) was refluxed in 200 mL of benzene and 150 mL of $SOCl_2$. The solution was concentrated and chased with toluene. The residue obtained was refluxed in 100 mL of ethanol for 20 minutes. The solvents were removed in vacuum to give the pure product. Light yellow oil; yield 72%; ^{1}H NMR

(CDCl3) δ 1.42 (t, J = 6.6 Hz, 3H), 4.43(q, J = 6.8Hz, 2H), 7.37 (br s, 1H), 8.18 (d, J = 6.6Hz, 1H), 8.54 (s, 1H); ^{13}C NMR δ 13.8, 61.8, 122.0, 126.9, 140.0, 149.5, 151.4, 164.2.

2-Chloro-nicotinic acid ethyl ester (2mmol, 0.343g) and 3,5-dimethoxyaniline (2mmol, 0.306g) were dissolved in ethylene glycol (10mL) and heated up to 160 °C with stirring. The reaction mixture was maintained at this temperature for 6h. HCL gas was formed during the course of the reaction. On cooling, the reaction mixture was poured into water (10 mL) and extracted with ether (4 X 100 mL). The ethereal layer was dried over MgSO4, evaporated and the residue was distilled at 162-165 °C/0.5 mm Hg. The compound was used in the next step without further purification. Yellow oil, yield 63%; ^{1}H NMR (CDCl3) δ 1.24 (t, *J* = 7.1 Hz, 3H), 3.78 (s, 6H), 4.11 (t, *J* = 7.1 Hz, 2H), 6.17 (s, 1H), 6.68 (t, *J* = 6.0 Hz, 1H), 6.97 (s, 2H), 8.20 (d, *J* = 7.7 Hz, 1H), 8.36 (s, 1H), 10.24 (s, 1H); ^{13}C NMR δ 20.7, 55.0, 60.1, 94.8, 98.7, 103.2, 107.1, 113.1, 139.9, 141.2, 152.7, 155.8, 160.7, 167.2, 170.9.

2-(3,5-Dimethoxy-phenylamino)-nicotinic acid ethyl ester (1.94mmol, 560mg) and 85% hydrazine hydrate (1.18 mL) and 2-propanol (2 mL) were refluxed for 3 h. On cooling the red solution deposited yellow solid that were filtered off and washed with little 2-propanol. Compound 1a appeared as yellow solid, 84% yield, ^{1}H NMR (DMSO-d6) δ 1.22 (br s, 2H), 4.00 (s, 6H), 6.18 (t, *J* = 2.2 Hz, 1H), 6.66–6.70 (m, 1H), 6.94 (s, 2H), 7.64 (dd, *J* = 1.8 Hz, 7.7 Hz, 1H), 7.70 (br s, 1H), 8.33 (dd, *J* = 1.5 Hz, 4.8 Hz), 10.1 (br s, 1H); ^{13}C NMR δ 55.3, 94.8, 98.7, 100.2, 103.4, 100.4, 109.5, 113.1, 135.1, 141.5, 151.8, 160.9, 169.1.



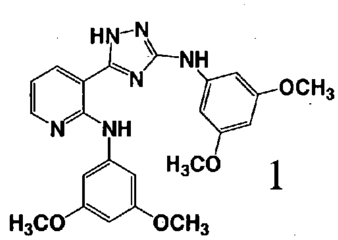
1b

N- (3,5-dimethoxyphenyl)-*S*-methylisothiourea hydroiodide (1b): A vigorously stirred hot solution of anhydrous ammonium thiocyanate (0.61 g, 7.8 mmol) in dry acetone (20 mL) was treated dropwise with 4-fluorobenzoyl chloride (1.03 g, 6.5 mmol). The reaction mixture was refluxed for 5 min. Then a solution of 3,5-dimethoxyaniline (1.0 g, 6.5 mmol) in dry acetone (10 mL) was added dropwise. The reaction mixture was heated for 1 h. The solvent was evaporated and water (50 mL) was added to residue. The precipitate was collected and recrystallized from ethyl

alcohol to give the product. White needles (ethanol), Yield 69%; ^{1}H NMR (DMSO) δ 3.76 (s, 6H), 6.43 (br s, 1H), 6.99 (br s, 2H), 7.35–7.41 (m, 2H), 8.04–8.09 (m, 2H), 11.62 (s, 1H) ; ^{13}C NMR (DMSO) δ . Anal. Calcd for $C_{16}H_{15}FN_2O_3S$: C, 57.47; H, 4.52; N, 8.38. Found: C, 57.49; H, 4.43; N, 8.26.

N-(3,5-Dimethoxyphenyl)-N'-(4-fluorobenzoyl)thiourea (1.5 g, 4.4 mmol) was heated to reflux with 5% aqueous NaOH (10 mL) for 15 min. The cooled reaction mixture was treated with concentrated HCl until acidic to precipitate both 4-fluorobenzoic acid and N-(3,5-dimethoxyphenyl)thiourea. The mixture was then made basic (pH 9) with concentrated NH_4OH to dissolve the 4-fluorobenzoic acid. The product was filtered and recrystallized from 95% ethyl alcohol to give pure product. White prisms, yield 75%; ^{1}H NMR (DMSO) δ 3.72 (s, 6H), 6.27 (br s, 1H), 6.62 (br s, 2H), 7.53 (br s, 2H), 9.66 (s, 1H); ^{13}C NMR (DMSO) δ 55.2, 96.4, 100.8, 140.6, 160.4, 180.7. Anal. Calcd for $C_9H_{12}N_2O_2S$: C, 50.92; H, 5.70; N, 13.20. Found: C, 50.88; H, 5.66; N, 12.96.

A solution of N-(3,5-dimethoxyphenyl)thiourea (0.53 g, 2.5 mmol) in freshly distilled dry methanol (10 mL) was treated with CH_3I (0.36 g, 2.5 mmol). The solution was refluxed for 2h, cooled, and evaporated to dryness in vacuo. The crystalline product was washed with several portion of ethyl ether and dried to give pure product. Compound 1b appeared as white microcrystals; yield 92%; ^{1}H NMR (DMSO) δ 2.70 (s, 3H), 3.78 (s, 6H), 6.53–6.56 (m, 3H), 9.30 (br s, 2H); ^{13}C NMR (DMSO) δ 55.6, 100.1, 103.7, 136.5, 161.1, 169.1.

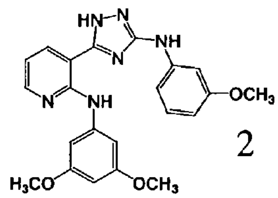


1

(3,5-Dimethoxy-phenyl)-{3-[5-(3,5-dimethoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (compound 1):

To a solution of 2-(3,5-dimethoxyphenylamino)nicotinic acid hydrazide (1a) (1mmol) and *N*- (3,5-dimethoxyphenyl)-*S*-methylisothiourea hydroiodide (1b) (1mmol) in 1 mL of pyridine were refluxed for 6 h. The cooled mixture was poured into crushed ice and extracted with ether. The solvent was removed and the crude product was recrystallized from ethyl acetate (and two drops of ethanol) to give the

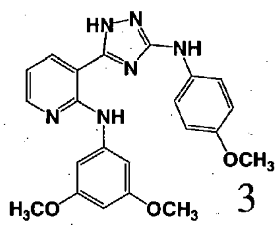
pure product. 1 appeared as a brown solid; yield 25%; ^{1}H NMR (DMSO-d6, 100 °C) δ 3.75 (s, 3H), 3.76 (s, 3H), 6.11 (br s, 1H), 6.18 (t, J = 2.2 Hz, 1H), 6.81 (d, J = 2.2 Hz, 2H), 6.89–6.93 (m, 1H), 7.07 (d, J = 1.8 Hz, 2H), 8.28–8.29 (m, 2H), 9.22 (br s, 1H), 10.7 (br s, 1H). MS m/z: 449 (M+1).



2

(3,5-Dimethoxy-phenyl)-{3-[5-(3-methoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (compound 2):

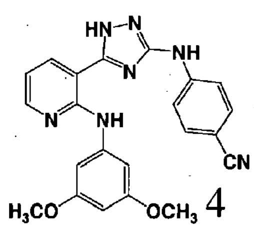
^{1}HNMR (DMSO-d6) 11.00 (s, 1H), 9.50 (s, 1H), 8.28-8.32 (m, 2H), 7.10-7.28 (m, 5H), 6.92-6.97 (m, 1H), 6.47-6.50 (m, 1H), 6.17-6.18 (t, 1H), 3.747-3.749 (d, 9H); MS m/z: 419 (M+1).



3

(3,5-Dimethoxy-phenyl)-{3-[5-(4-methoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 3):

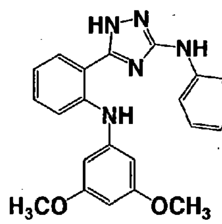
^{1}HNMR (methanol-d4) δ 8.25-8.35 (br s, 1H), 8.19 (s, 1H), 7.41-7.45 (d, 2H), 6.83-6.96 (m, 5H), 6.16 (s, 1H), 3.3-3.80 (m, 9H); MS m/z: 419 (M+1).



4

4-{5-[2-(3,5-Dimethoxy-phenylamino)-pyridin-3-yl]-1H-[1,2,4]triazol-3-ylamino}-benzonitrile (Compound 4):

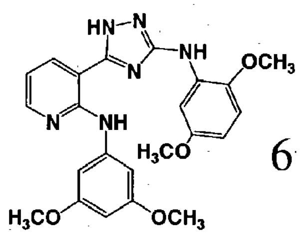
^{1}HNMR (DMSO-d6) δ 10.30 (s, 1H), 8.32-8.46 (m, 2H), 7.78-7.93 (m, 4H), 7.00-7.77 (m, 3H), 6.25-6.27 (d, 1H, J=0.069), 3.80-3.82 (d, 6H, J=0.033Hz); MS m/z: 414 (M+1).



5

{5-[2-(3,5-Dimethoxy-phenylamino)-phenyl]-1H-[1,2,4]triazol-3-yl}-phenyl-amine (Compound 5):

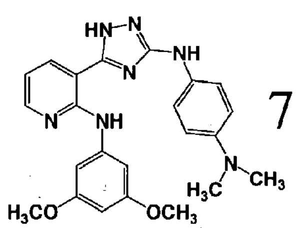
^{1}HNMR (DMSO-d6) δ 10.50 (s, 1H), 9.66 (s, 1H), 9.59 (s, 1H), 8.14-8.32 (m, 2H), 7.48-7.55 (m, 2H), 7.16 (s, 1H), 6.78-7.09 (m, 5H), 6.08 (1H), 3.65 (s, 6H); MS m/z: 389(M+1).



6

(3,5-Dimethoxy-phenyl)-{3-[5-(2,5-dimethoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 6):

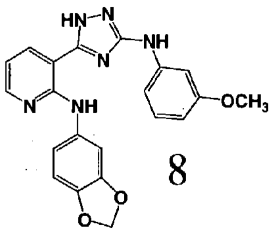
^{1}HNMR (CDCl3) δ 10.34 (s, 1H), 8,27-8.29 (m, 2H), 7.77-7.78 (d, 1H, J=0.03Hz), 7.36 (s, 1H), 7.00-7.01 (d, 2H, J=0.03), 6.73-6.82 (m, 2H), 6,45-6.49 (m, 1H), 6.14-6.15 (t, 1H, J=045Hz), 3.77-3.83 (m, 12H); MS m/z: 449 (M+1).



7

(3,5-Dimethoxy-phenyl)-{3-[5-(4-aminodimethyl-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 7):

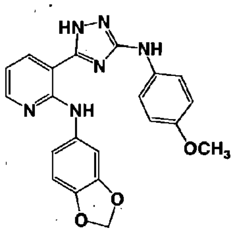
^{1}HNMR (CDCl3) δ 10.56 (s, 1H), 8.43-8.50 (m, 2H), 7.45-7.49 (d, 3H), 6.94-6.98 (m, 4H), 6.36-6.38 (m, 1H), 3.98-4.03 (t, 6H), 3.19 (br s, 6H); MS m/z: 432 (M+1).



8

Benzo[1,3]dioxol-5-yl-{3-[5-(3-methoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 8):

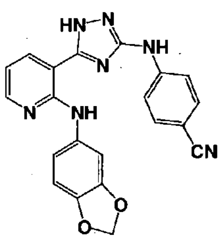
^{1}HNMR (CDCl3) δ 10.19 (s, 1H), 8.22-8.24 (m, 1H), 8.11 (br s, 1H), 6.60-7.39 (m, 10H), 5.91 (s, 2H), 3.81-3.85 (t, 3H); MS m/z: 403 (M+1).



9

Benzo[1,3]dioxol-5-yl-{3-[5-(4-methoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 9):

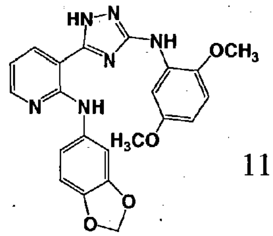
^{1}HNMR (CDCl3) δ 10.07 (s, 1H), 8.09-8.16 (m, 2H), 7.31-7.35 (m, 1H), 7.22-7.30 (m, 3H), 6.88-6.95 (m, 3H),), 6,62-6.75 (m, 3H), 5.84-5.86 (d, 2H), 3.78 (s, 3H); MS m/z: 403 (M+1).



10

4-{5-[2-(Benzo[1,3]dioxol-5-ylamino)-pyridin-3-yl]-1H-[1,2,4]triazol-3-ylamino}-benzonitrile (Compound 10):

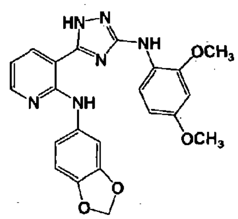
^{1}HNMR (DMSO-d6) δ 10.77 (br s, 1H), 10.18 (s, 1H), 8.30-8.32 (d, 2H, J=0.06Hz), 7.78 (s, 4H), 7.61-7.62 (d, 1H, J=0.021), 1.73-7.16 (t, 1H, J=0.028), 6.94-6.97 (m, 2H), 6.06-6.05 (d, 2H, J=0.036); MS m/z: 398 (M+1).



11

Benzo[1,3]dioxol-5-yl-{3-[5-(2,5-dimethoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 11):

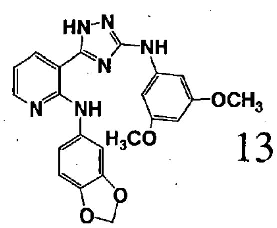
^{1}HNMR (DMSO-d6) δ 10.49 (s, 1H), 8.88 (s, 1H), 8.25-8.40 (m, 2H), 7,95 (s, 1H), 7.64 (s, 1H), 6.91-7.13 (m, 4H), 6.49-6.58 (m, 1H), 6.03-6.06 (d, 2H), 3.69-3.89 (m, 6H); MS m/z: 433 (M+1).



12

Benzo[1,3]dioxol-5-yl-{3-[5-(2,4-dimethoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 12):

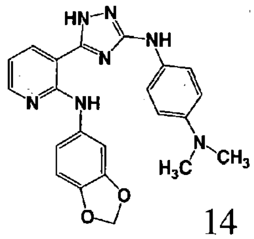
^{1}HNMR (methanol-d4) δ 8.32 (s, 1H), 8.09 (s, 1H), 7.34 (s, 1H), 6.88-7.00 (m, 1H), 6.70-6.80 (m, 3H), 6.50-6.70 (m, 2H), 5.90 (d, 2H), 3.71-3.89 (m, 6H); MS m/z: 433 (M+1).



13

Benzo[1,3]dioxol-5-yl-{3-[5-(3,5-dimethoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 13):

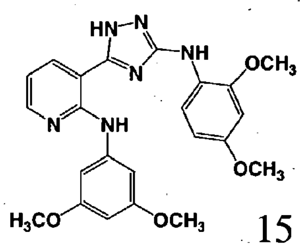
^{1}HNMR (methanol-d4) δ 8.09-8.21 (m, 2H), 7.30-7.38 (m, 1H), 6.95-6.99 (m, 1H), 6.69-6.82 (m, 5H), 6.09 (s, 1H), 5.88 (s, 2H), 3.70-3.74 (m, 6H); MS m/z: 433 (M+1).



14

Benzo[1,3]dioxol-5-yl-{3-[5-(4-aminodimethyl-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 14):

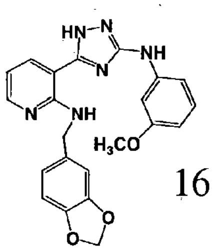
^{1}HNMR (DMSO-d6) δ 13.28 (s, 1H), 11.07 (s, 1H), 9.27 (s, 1H), 8.23-8.34 (m, 2H), 6.79-7.60 (m, 8H), 6.03 (s, 2H), 2.71 (s, 6H); MS m/z: 416 (M+1).



15

(3,5-Dimethoxy-phenyl)-{3-[5-(2,4-dimethoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 15):

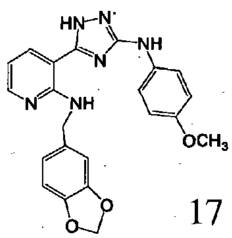
^{1}HNMR (CDCl3) δ 10.41 (s, 1H), 8.19-8.29 (m, 2H), 7.77-7.80 (m, 1H), 7.03-7.04 (d, 3H), 6.72-6.76 (m, 1H), 6.51-6.55 (m, 2H), 6.14-6.16 (m, 1H), 3.64-3.90 (m, 12H); MS m/z: 449 (M+1).



16

Benzo[1,3]dioxol-5-ylmethyl-{3-[5-(3-methoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 16):

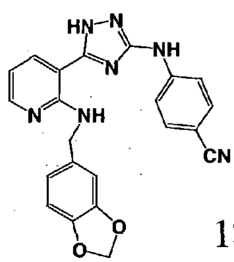
^{1}HNMR (DMSO-d6) δ 9.64 (s, 1H), 9.29 (s, 1H), 8.91 (s, 1H), 8.14-8.33 (m, 2H), 6.73-7.28 (m, 7H), 6.44-6.56 (m, 1H), 6.01 (s, 2H), 4.70 (s, 2H), 3.75-3.78 (d, 3H, J=0.078Hz); MS m/z: 417 (M+1).



17

Benzo[1,3]dioxol-5-ylmethyl-{3-[5-(4-methoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 17):

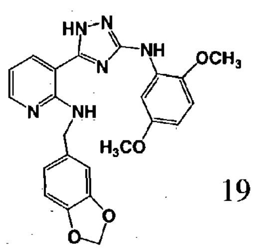
^{1}HNMR (DMSO-d6) δ 9.37 (s, 1H), 8.91-9.02 (d, 1H, J=0.33Hz), 8.15-8.36 (m, 3H), 7.45-7.48 (d, 2H), 6.65-6.98 (m, 6H), 6.02 (s, 2H), 4.69 (s, 2H), 3.76 (s, 3H); MS m/z: 417 (M+1).



18

4-(5-{2-[(Benzo[1,3]dioxol-5-ylmethyl)-amino]-pyridin-3-yl}-1H-[1,2,4]triazol-3-ylamino)-benzonitrile (Compound 18):

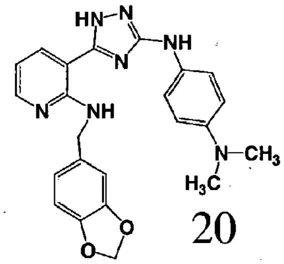
^{1}HNMR (DMSO-d6) δ 13.78 (s, 1H), 9.78 (s, 1H), 8.46 (s, 1H), 7.90-7.97 (m, 2H), 7.31-7.48 (m, 4H), 6.50-6.83 (m, 4H), 5.83 (s, 2H), 4.43 (s, 2H); MS m/z: 412 (M+1).



19

Benzo[1,3]dioxol-5-ylmethyl-{3-[5-(2,5-dimethoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 19):

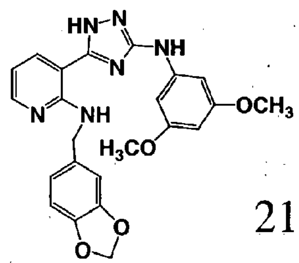
^{1}HNMR (DMSO-d6) δ 7.70-7.78 (m, 2H), 7.45 (s, 1H), 7.30-7.35(m, 1H), 7.0-7.06 (m, 2H), 6.60-6.68 (m, 2H), 5.61-6.12 (m, 3H), 560-5.65(m, 1H), 5.06 (s, 2H), 3.77 (s, 2H), 2.93-3.02 (d, 6H); MS m/z: 447 (M+1).



20

Benzo[1,3]dioxol-5-ylmethyl-{3-[5-(4-aminodimethyl-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 20):

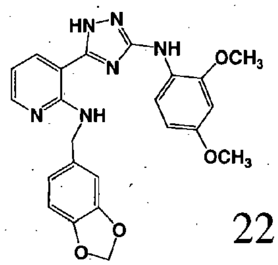
^{1}HNMR (methanol-d4) δ 8.16-8.19 (m, 1H), 8.01-8.03 (m, 1H), 7.20-7.23 (m, 2H), 6.62-6.84 (m, 6H), 5.87 (s, 2H), 4.58(s, 2H), 2.83-2.86 (m, 6H); MS m/z: 430(M+1).



21

Benzo[1,3]dioxol-5-ylmethyl-{3-[5-(3,5-dimethoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 21):

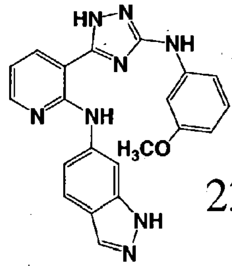
^{1}HNMR (methanol-d4) δ 8.02-8.15 (m, 2H), 6.69-6.81 (m, 2H), 6.60-6.67 (m, 4H), 6.04 (s, 1H), 5.45-5.87 (m, 2H), 4.57 (s, 2H), 3.69-3.73 (d, 6H); MS m/z: 447 (M+1).



22

Benzo[1,3]dioxol-5-ylmethyl-{3-[5-(2,4-dimethoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 22):

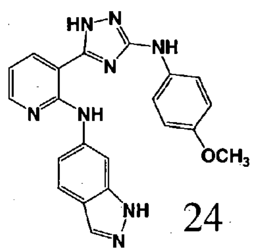
^{1}HNMR (DMSO-D6) δ 12.20 (s, 1H), 8.04-8.23 (m, 4H), 7.81-7.90 (m, 1H), 6.82-6.97 (d, 3H), 6.67-6.78 (m, 2H), 6.44-6.48 (d, 1H, J=0.24Hz), 6.01 (s, 2H), 4.55-4.59 (m, 2H), 3.67-3.88 (m, 6H); MS m/z: 447 (M+1).



23

(1H-Indazol-6-yl)-{3-[5-(3-methoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 23):

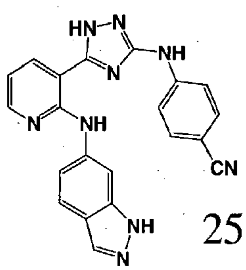
[1]HNMR (Acetone-d6) δ 8.78-8.95 (m, 2H), 8.30-8.60 (m, 2H), 7,95 (s, 1H), 7.65-7.70 (m, 1H), 7.44-7.48 (m, 1H), 7.10-7.38 (m, 3H), 6.91-6.98 (m, 1H), 6.55-6.65 (m, 1H), 3.90 (s, 3H); MS m/z: 399(M+1).



24

(1H-Indazol-6-yl)-{3-[5-(4-methoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 24):

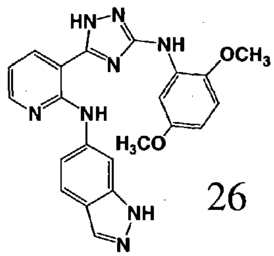
[1]HNMR (methanol-d4) δ 8.51 (s, 1H), 8.23-8.50 (m, 2H), 7.91-7.94 (s, 1H), 7.61-7.65 (m, 1H), 7.40-7.46 (m, 2H), 6.85-7.08 (m, 4H), 3.65 (s, 3H); MS m/z: 399(M+1).



25

4-{5-[2-(1H-Indazol-6-ylamino)-pyridin-3-yl]-1H-[1,2,4]triazol-3-ylamino}-benzonitrile (Compound 25):

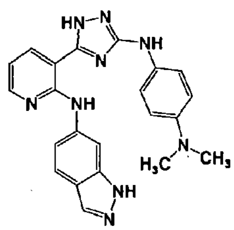
[1]HNMR (DMSO-d6) δ 14.26 (s, 1H), 12.96 (s, 1H), 11.24 (s, 1H), 10.17 (s, 1H), 8.35-8.72 (m, 3H), 7.58-8.14 (m, 6H), 5.05-7.22 (m, 2H); MS m/z: 394(M+1).



26

{3-[5-(2,5-Dimethoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-(1H-indazol-6-yl)-amine (Compound 26):

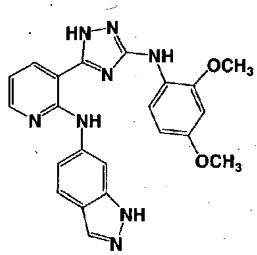
^{1}HNMR (methanol-d4) δ 8.45 (s, 1H), 8.35-8.37 (d, 1H, J=0.057Hz), 8.23-8.26 (m, 1H), 7.88-7.91 (m, 2H), 7.61-7.64 (m, 1H), 7.04-7.08 (m, 1H), 6.87-6.92 (m, 2H), 5.50-6.54 (m, 1H), 3.88(s, 3H), 3.77 (s, 3H); MS m/z: 429 (M+1).



27

(1H-Indazol-6-yl)-{3-[5-(4-aminodimethyl-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 27):

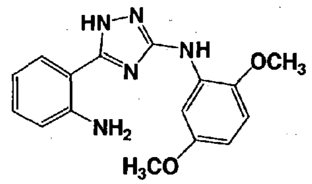
^{1}HNMR (methanol-d4) δ 8.55 (s, 1H), 8.32-8.38 (m, 1H), 8.23-8.25 (m, 1H), 7.90-7.93 (t, 1H), 7.60-7.63 (m, 1H), 7.34-7.38 (m, 2H), 7.05-7.08 (m, 1H), 6.85-6.90 (m, 3H), 2.87-2.94 (m, 6H); MS m/z: 412 (M+1).



28

{3-[5-(2,4-Dimethoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-(1H-indazol-6-yl)-amine (Compound 28):

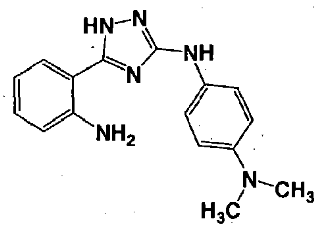
^{1}HNMR (methanol-d4) δ 8.496 (s, 1H), 8.33-8.35 (m, 1H), 8.22-8.25 (m, 1H), 7.906-7.908 (d, 1H), 7.779-7.808 (d, 1H), 7.607-7.636 (d, 1H), 7.01-7.06 (m, 1H), 6.85-6.89 (m, 1H), 6.55-6.65 (m, 2H), 3.81-3.89 (m, 6H); MS m/z: 429 (M+1).



29

[5-(2-Amino-phenyl)-1H-[1,2,4]triazol-3-yl]-(2,5-dimethoxy-phenyl)-amine (Compound 29):

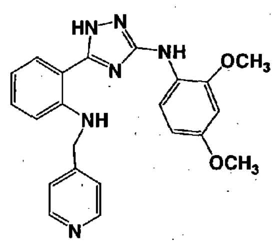
[1]HNMR (methanol-d4) δ 7.83-7.84 (d, 1H), 7.70-7.73 (d, 1H), 7.12-7.18 (m, 1H), 6.81-6.88 (m, 2H), 6.70-6.73 (m, 1H), 6.41-6.45 (m, 1H), 3.77-3.87 (d, 6H); MS m/z: 312 (M+1).



30

[5-(2-Amino-phenyl)-1H-[1,2,4]triazol-3-yl]-(4-aminodimethyl-phenyl)-amine (Compound 30):

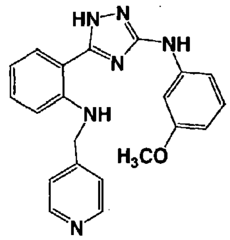
[1]HNMR (methanol-d4) δ 7.71-7.74 (d, 1H), 7.30-7.33 (d, 2H), 7.09-7.15 (m, 1H), 6.79-6.84 (m, 3H), 6.66-6.71 (m, 1H), 2.83-2.85 (d, 6H); MS m/z: 295 (M+1). C



31

(2,4-Dimethoxy-phenyl)-(5-{2-[(pyridin-4-ylmethyl)-amino]-phenyl}-1H-[1,2,4]triazol-3-yl)-amine (Compound 31):

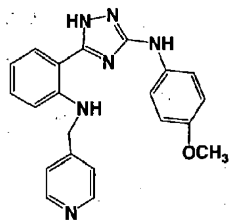
[1]HNMR (DMSO-d6) δ 13.41 (s, 1H), 12.12 (s, 1H), 8.75 (s, 1H), 7.82-8.55 (m, 4H), 7.73-7.33 (m, 2H), 7.15 (s, 1H), 6.40-6.75 (m, 4H), 4.55 (s, 2H), 3.82-3.96 (d, 6H); MS m/z: 403 (M+1).



32

(3-Methoxy-phenyl)-(5-{2-[(pyridin-4-ylmethyl)-amino]-phenyl}-1H-[1,2,4]triazol-3-yl)-amine (Compound 32):

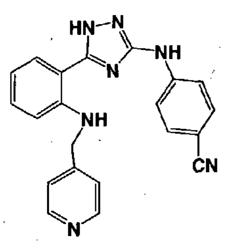
^{1}HNMR (methanol-d4) δ 8.40-8.45 (m, 2H), 7.74-7.80 (m, 1H), 7.42-7.45 (d, 2H), 7.08-7.35 (m, 3H), 6.94-6.98 (m, 3H), 6.95-6.98 (m, 1H), 4.59 (s, 2H), 3.75 (s, 3H); MS m/z: 373 (M+1).



33

(4-Methoxy-phenyl)-(5-{2-[(pyridin-4-ylmethyl)-amino]-phenyl}-1H-[1,2,4]triazol-3-yl)-amine (Compound 33):

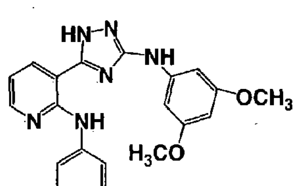
^{1}HNMR (DMSO-d6) δ 8.55-9.35 (m, 3H), 7.80-8.20 (m, 2H), 7.20-7.55 (m, 5H), 6.61-6.96 (m, 4H), 4.79 (s, 2H), 3.80 (s, 3H); MS m/z: 373 (M+1).



34

4-(5-{2-[(Pyridin-4-ylmethyl)-amino]-phenyl}-1H-[1,2,4]triazol-3-ylamino)-benzonitrile (Compound 34):

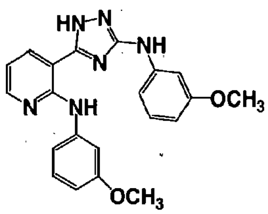
^{1}HNMR (DMSO-d6) δ 11.39 (s, 1H), 8.00-8.57 (m, 3H), 7.68-7.98 (m, 6H), 7.36-7.41 (m, 3H), 6.74-6.83 (m, 2H), 4.70-4.72 (d, 2H); MS m/z: 369 (M+1).



35

{3-[5-(3,5-Dimethoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-phenyl-amine (Compound 35):

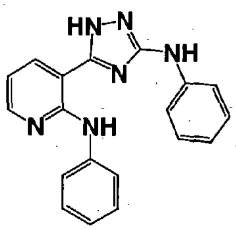
[1]HNMR (DMSO-d6) δ 8.28 (s, 1H), 8.16-8.17 (d, 1H), 7.71-7.74 (d, 2H), 7.26-7.32 (t, 2H), 6.96-7.01 (t, 1H), 6.76-6.85 (m, 3H), 6.13 (s, 1H), 3.69-3.78 (m, 6H); MS m/z: 389 (M+1).



36

(3-Methoxy-phenyl)-{3-[5-(3-methoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 36):

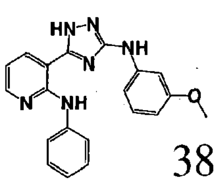
[1]HNMR (methanol-d4) δ 8.36 (s, 1H), 8.32-8.33 (m, 1H), 7.51 (s, 1H), 7.16-7.25 (m, 4H), 7.03-7.07 (m, 1H),, 6.85-6.90 (m, 1H), 6.52-6.60 (m, 2H), 3.78-3.80 (d, 6H); MS m/z: 389 (M+1).



37

Phenyl-[3-(5-phenylamino-2H-[1,2,4]triazol-3-yl)-pyridin-2-yl]-amine (Compound 37):

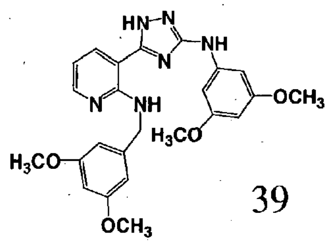
[1]HNMR (DMSO-d6) δ 13.55 (s, 1H), 11.0 (s, 1H), 9.6 (s, 1H), 8.25-8.44 (m, 2H), 7.00-7.91 (m, 11H); MS m/z: 329(M+1).



38

{3-[5-(3-Methoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-phenyl-amine (Compound 38):

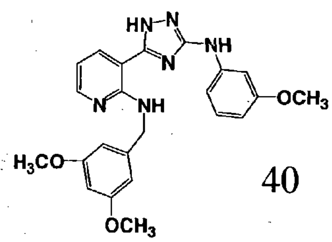
[1]HNMR (DMSO-d6) δ 8.34 (s, 1H), 7.89 (s, 1H), 6.96-7.40 (m, 9H), 6.60 (s, 1H), 3.74-3.80(m, 3H); MS m/z: 359 (M+1).



39

(3,5-Dimethoxy-benzyl)-{3-[5-(3,5-dimethoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 39):

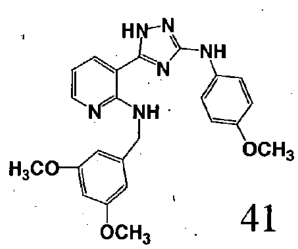
^{1}HNMR (DMSO-d6) δ 8.13 (s, 1H), 6.65-6.88 (m, 4H), 6.51 (s, 2H), 6.35 (s, 2H), 6.05 (s, 1H), 4.75 (s, 2H), 3,75 (m, 12H); MS m/z: 463(M+1).



40

(3,5-Dimethoxy-benzyl)-{3-[5-(3-methoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 40):

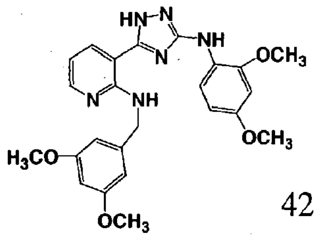
^{1}HNMR (DMSO-d6) δ 13.35 (s, 1H), 9.45(s, 1H), 8.12 (s, 2H), 7.06-7.25 (m, 2H), 6.70-6.74 (m, 1H), 6.37-6.51 (m, 4H), 4.70-4.72 (d, 2H), 3.62-3.72 (m, 9H); MS m/z: 433 (M+1).



41

(3,5-Dimethoxy-benzyl)-{3-[5-(4-methoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 41):

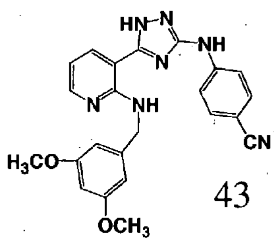
^{1}HNMR (DMSO-d6) δ 13.25 (s, 1H), 9.32 (s, 1H), 8.92-8.99 (d, 1H), 8.08-8.39 (m, 2H), 7.40-7.45 (m, 2H), 6.38 –6.86 (m, 6H), 4.66-4.73 (m, 2H), 3.68-3.71 (m, 9H); MS m/z: 433 (M+1).



42

(3,5-Dimethoxy-benzyl)-{3-[5-(2,4-dimethoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 42):

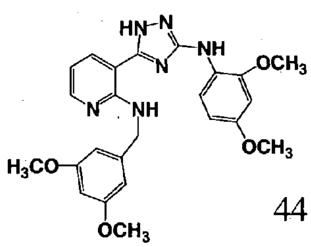
^{1}HNMR (DMSO-d6) δ 12.17 (s, 1H), 8.09-8.66 (m, 4H), 7.85-7.98 (m, 1H), 6.27-6.70 (m, 6H), 4.67-4,70 (m, 2H), 3.65-3.90 (m, 12H); MS m/z: 463 (M+1).



43

4-{5-[2-(3,5-Dimethoxy-benzylamino)-pyridin-3-yl]-1H-[1,2,4]triazol-3-ylamino}-benzonitrile (Compound 43):

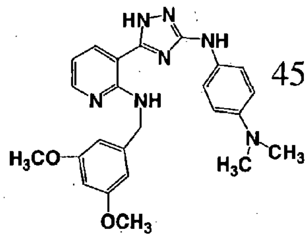
^{1}HNMR (DMSO-d6) δ 11.76 (s, 1H), 10.02 (s, 1H), 8.74 (s, 1H), 8.14-8.18 (m, 2H), 7.61 (m, 4H), 6.72-6.77 (m, 1H), 6.38-6.52 (m, 3H), 4.70-4.71 (d, 2H), 3.70 (s, 6H); MS m/z: 428 (M+1).



44

(3,5-Dimethoxy-benzyl)-{3-[5-(2,4-dimethoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 44):

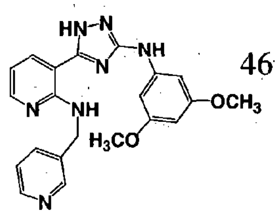
^{1}HNMR (DMSO-d6) δ 8.72 (s, 1H), 8.25-8.28 (m, 2H), 8.09-8.16 (m, 1H), 7.99-8.00 (d, 1H), 7.79-7.80 (t, 1H), 6.87-6.96 (m, 1H), 6.70-6.75 (m, 1H), 6.35-6.52 (m, 4H), 4.69-4.71 (d, 2H), 3.69-3.83 (m, 12H); MS m/z: 463 (M+1).



45

(3,5-Dimethoxy-benzyl)-{3-[5-(4-aminodimethyl-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-amine (Compound 45):

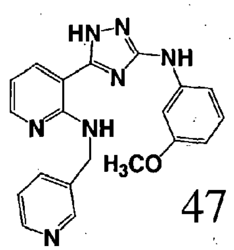
^{1}HNMR (DMSO-d6) δ 9.11 (s, 1H), 8.42 (s, 1H), 8.10-8.20 (d, 2H), 7.31-7.434 (d, 2H), 6.38-6.67 (m, 6H), 4.69 (s, 2H), 3.69 (s, 6H), 2.81 (s, 6H); MS m/z: 446 (M+1).



46

{3-[5-(3,5-Dimethoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-pyridin-3-ylmethyl-amine (Compound 46):

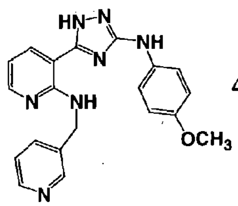
^{1}HNMR (DMSO-d6) δ 8.58 (s, 1H), 8.42-8.45 (m, 1H), 8.10-8.25 (m, 2H), 7.67-7.75 (m, 1H), 7.30-7.40 (m, 2H), 6.70-6.82 (m, 2H), 6.00-6.05 (d, 1H), 4.76-4.84 (d, 2H), 3.70-3.75 (m, 6H) ; MS m/z: 404 (M+1).



47

{3-[5-(3-Methoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-pyridin-3-ylmethyl-amine (Compound 47):

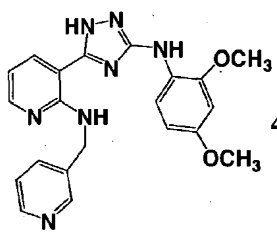
^{1}HNMR (methanol-d4) δ 8.45 (s, 1H), 8.26-8.28 (m, 1H), 8.07-8.08 (m, 1H), 7.93-7.95 (m, 1H), 7.72-7.74 (d, 1H), 7.21-7.26 (m, 1H), 6.99-7.08 (m, 2H), 6.83-6.86 (m, 1H), 6.56-6.61 (m, 1H), 6.37-6.40 (m, 1H), 4.69 (s, 2H), 3.65 (s, 3H); MS m/z: 374 (M+1).



48

{3-[5-(4-Methoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-pyridin-3-ylmethyl-amine (Compound 48):

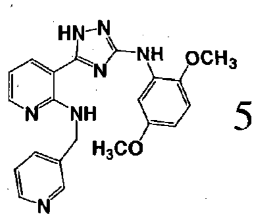
[1]HNMR (DMSO-d6) δ 9.19 (s, 1H), 8.60-8.61 (d, 1H), 8.43-8.48 (m, 1H), 8.12-8.20 (m, 2H), 7.74-7.77 (m, 1H), 7.33-7.44 (m, 3H), 6.70-6.85 (m, 3H) 4.77-4.79 (d, 2H), 3.71 (s, 3H); MS m/z: 374 (M+1).



49

{3-[5-(2,4-Dimethoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-pyridin-3-ylmethyl-amine (Compound 49):

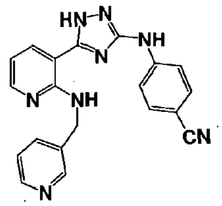
[1]HNMR (DMSO-d6) δ 8.59 (s, 1H), 8.44-8.46 (m, 2H), 8.21 (br, s, 1H), 8.09-8.10 (m, 1H), 7.85-7.88 (m, 1H), 7.73-7.88 (m, 1H), 7.31-7.36 (m, 1H), 6.63-6.73 (m, 2H), 6.44-6.69 (m, 1H), 4.76-4.78 (m, 2H), 3.67-3.84 (m, 6H); MS m/z: 404 (M+1).



50

{3-[5-(2,5-Dimethoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-pyridin-3-ylmethyl-amine (Compound 50):

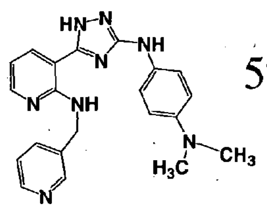
[1]HNMR (DMSO-d6) δ 8.10-8.12 (m, 2H), 7.93-7.94 (m, 2H), 7.71-7.74 (m, 1H), 7.30-7.36 (m, 1H), 6.92-6.95 (m, 1H), 6.71-6.76 (m, 1H), 6.43-6.47 (m, 1H), 4,78-4.80 (d, 2H), 3.71-3.83 (m, 6H); MS m/z: 404 (M+1).



51

4-(5-{2-[(Pyridin-3-ylmethyl)-amino]-pyridin-3-yl}-1H-[1,2,4]triazol-3-ylamino)-benzonitrile (Compound 51):

[1]HNMR (DMSO-d6) δ 10.06 (s, 1H), 8.77-8.79 (d, 1H), 8.45-8.47 (m, 1H), 8.17-8.26 (m, 2H), 7.66-7.84 (m, 5H), 7.32-7.37 (m, 1H), 6.74-6.79 (m, 1H), 4.79-4.81 (d, 2H); MS m/z: 369 (M+1).

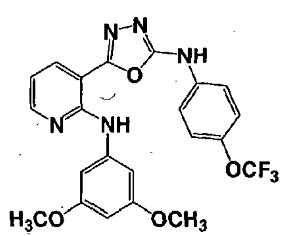


52

{3-[5-(4-Aminodimethyl-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}-pyridin-3-ylmethyl-amine (Compound 52):

[1]HNMR (DMSO-d6) δ 9.02 (s, 1H), 8.60-8.61 (d, 1H), 8.46-8.47 (m, 1H), 8.10-8.19 (m, 2H), 7.74-7.77 (d, 1H), 7.30-7.37 (m, 3H), 6.66-6.74 (m, 3H), 4.77-4.79 (d, 2H), 2.82 (s, 6H); MS m/z: 387 (M+1).

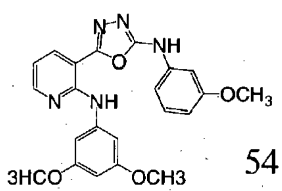
Example 2: synthesis of (3,5-Dimethoxy-phenyl)-{3-[5-(4-trifluoromethoxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 53).



53

To a solution of intermediate hydrazide (1a) (1.0g, 3.48 mmol) in dichloromethane (20 mL) added 4-trifluoromethoxy phenyl isothiocyanate (0.64 mL, 3.83 mmol). The reaction mixture was refluxed for 2 hours under argon. Cooled down and solid precipitated from the solution, filtered; the solid was washed with ether to

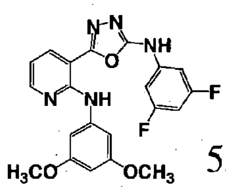
provide a yellow solid 1.489 g. Yield: 93%. ^{1}H NMR (DMSO-d6) δ 10.95 (s, 1H), 10.71 (s, 1H), 9.93-9.96 (m, 2H), 8.45-8.48 (m, 1H), 8.25-8.28 (m, 1H), 7.60-7.66 (m, 2H), 7.35-7.42 (m, 2H), 6.90-7.05 (m, 3H), 6.20 (s, 1H), 3.80 (s, 6H). MS m/z: 508. To this yellow solid (1.45 g, 2.86 mmol) in toluene (20 mL) added 1,3-dicyclohexylcarbodiimide (0.885 g, 4.3 mmol). Then the reaction mixture was refluxed for 5 hours. The reaction mixture was diluted with ethyl acetate (50 mL), which was washed with sodium bicarbonate aqueous solution (30 mL), brine (30 mL, twice). The organic layer was separated and dried over anhydrous sodium sulfate. Filtered and evaporated to get a solid. This solid was washed with warm methanol to get a white solid 1.1 g (81.5% yield). ^{1}HNMR (DMSO-d6) δ 11.10 (s, 1H), 10.06 (s, 1H), 8.42-8.44 (m, 1H), 8.06-8.09 (m, 1H), 7.76-7.80 (m, 2H), 7.43-7.46 (d, 2H), 7.04-7.08 (m, 3H), 6.25-6.26 (t, 1H), 3.81 (t, 6H). MS m/z: 474 (M+1).



54

(3,5-Dimethoxy-phenyl)-{3-[5-(3-methoxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 54):

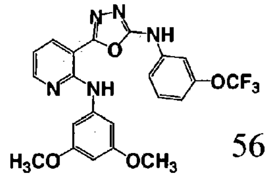
^{1}HNMR (DMSO-d6) δ 10.89 (s, 1H), 10.20 (s, 1H), 8.33-8.38 (m, 1H), 8.01-8.04 (m, 1H), 7.22-7.33 (m, 2H), 7.10-7.22 (m, 1H), 7.01-7.09 (m, 3H), 6.62-6.69 (m, 1H), 6.21-6.25 (m, 1H), 3.78-3.87 (m, 9H); MS m/z: 420 (M+1).



55

{3-[5-(3,5-Difluoro-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-(3,5-dimethoxy-phenyl)-amine (Compound 55):

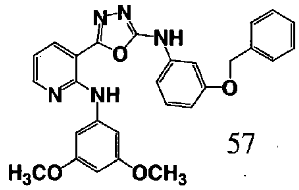
^{1}HNMR (DMSO-d6) δ 11.40 (s, 1H), 10.0 (s, 1H), 8.40-8.43 (m, 1H), 8.01-8.04 (m, 1H), 7.01-7.06 (m, 2H), 6.81-6.95 (m, 4H), 6.23-6.25 (t, 1H), 3.80 (s, 6H); MS m/z: 426 (M+1).



56

(3,5-Dimethoxy-phenyl)-{3-[5-(3-trifluoromethoxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 56):

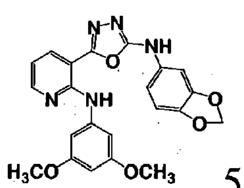
[1]HNMR (DMSO-d6) δ 11.34 (s, 1H), 10.02 (s, 1H), 8.43-8.45 (m, 1H), 8.06-8.16 (m, 2H), 7.87-7.90 (m, 1H), 7.64-7.70 (t, 1H), 7.43-7.46 (d, 1H), 7.05-7.10 (m, 3H), 6.25-6.27 (t, 1H), 3.81 (s, 6H); MS m/z: 474 (M+1).



57

{3-[5-(3-Benzyloxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-(3,5-dimethoxy-phenyl)-amine (Compound 57):

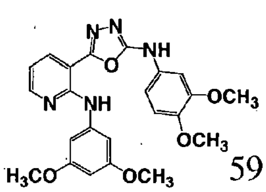
[1]HNMR (DMSO-d6) 10.93 (s, 1H), 10.07 (s, 1H), 8.41-8.44 (m, 1H), 8.04-8.07 (m, 1H), 7.05-7.58 (m, 11H), 6.74-6.77 (m, 1H), 6.24-6.26 (t, 1H), 5.16 (s, 2H), 2.80 (s, 6H). MS m/z: 496 (M+1).



58

{3-[5-(Benzo[1,3]dioxol-5-ylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-(3,5-dimethoxy-phenyl)-amine (Compound 58):

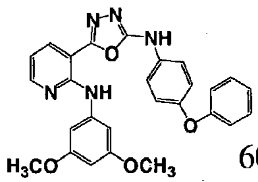
[1]HNMR (DMSO-d6) δ 10.76 (s, 1H), 10.07 (s, 1H), 8.40-8.43 (m, 1H), 8.02-8.05 (m, 1H), 7.33-7.34 (d, 1H), 6.94-7.11 (m, 5H), 6.24-6.26 (t, 1H), 6.05 (s, 2H), 3.77-3.80 (d, 6H); MS m/z: 434 (M+1).



59

(3,5-Dimethoxy-phenyl)-{3-[5-(3,4-dimethoxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 59):

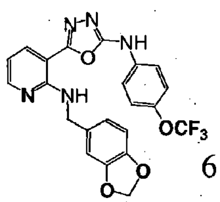
[1]HNMR (DMSO-d6) δ 10.68 (s, 1H), 10.04 (s, 1H), 8.40-8.42(t, 1H), 8.03-8.06 (t, 1H), 7.35-7.36 (d, 1H), 7.00-7.19 (m, 5H), 6.25 (s, 1H), 3.78-3.82 (m, 12H); MS m/z: 450 (M+1).



60

(3,5-Dimethoxy-phenyl)-{3-[5-(4-phenoxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 60):

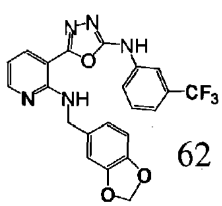
[1]HNMR (DMSO-d6) δ10.86 (s, 1H), 10.05 (s, 1H), 8.35-8.37 (m, 1H), 8.00-8.02 (m, 1H), 7.65-7.68 (d, 2H), 7,34-7.40 (t, 2H), 6.96-7.12 (m, 8H), 6.19-6.20 (t, 1H), 3.72-3.76 (d, 6H); MS m/z: 482 (M+1).



61

Benzo[1,3]dioxol-5-ylmethyl-{3-[5-(4-trifluoromethoxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 61):

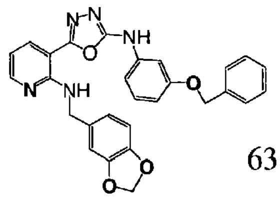
[1]HNMR (DMSO-d6) δ11.05 (s, 1H), 8.28-8.30 (s, 1H), 8.11-8.16 (t, 1H), 7.92-7.96 (m, 1H), 7.73-7.76 (d, 2H), 7.17-7.29 (m, 1H), 7.00 (s, 1H), 6.91 (s, 2H), 6.80-6.84 (m, 1H), 6.02 (s, 2H), 4.70-4.72 (d, 2H); MS m/z: 472 (M+1).



62

Benzo[1,3]dioxol-5-ylmethyl-{3-[5-(3-trifluoromethyl-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 62):

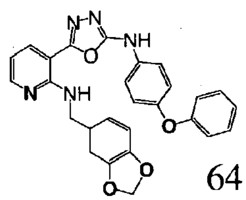
[1]HNMR (DMSO-d6) δ 11.22 (s, 1H), 8.28-8.31 (m, 1H), 8.15 (s, 2H), 7.91-7.95 (m, 1H), 7.81-7.84 (d, 1H), 7.64-7.67 (t, 1H), 7.40-7.42 (d, 1H), 6.80-7.00 (m, 4H), 6.02 (s, 2H), 4.71-4.73 (d, 2H); MS m/z: 456 (M+1).



63

Benzo[1,3]dioxol-5-ylmethyl-{3-[5-(3-benzyloxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 63):

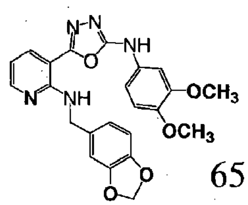
[1]HNMR (DMSO-d6) δ 10.83 (s, 1H), 8.27-8.30 (m, 1H), 8.12-8.16 (m, 1H), 7.90-7.94 (m, 1H), 7.17-7.52 (m, 9H), 7.00 (s, 1H), 6.90 (d, 3H), 6.71-6.84 (m, 2H), 6.02 (s, 1H), 5.14 (s, 1H), 4.71-4.73 (d, 2H); MS m/z: 494 (M+1).



64

(4,5-Dihydro-benzo[1,3]dioxol-5-ylmethyl)-{3-[5-(4-phenoxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 64):

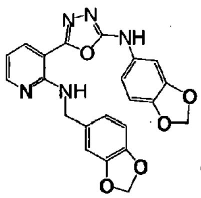
[1]HNMR (DMSO-d6) δ 10.81 (s, 1H), 8.27-8.29 (m, 1H), 8.13-8.17 (t, 1H), 7.92-7.95 (m, 1H), 7.66-7.69 (m, 2H), 7.38-7.43 (t, 2H), 6.79-7.16 (m, 9H), 6.02 (s, 2H), 4.70-4.72 (m, 2H); MS m/z: 483 (M+1).



65

Benzo[1,3]dioxol-5-ylmethyl-{3-[5-(3,4-dimethoxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 65):

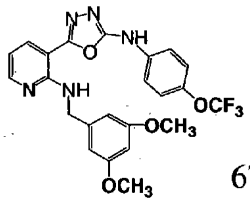
[1]HNMR (DMSO-d6) δ10.60 (s, 1H), 8.26-8.29 (m, 1H), 8.15-8.17 (t, 1H), 7.89-7.93 (m, 1H), 7.38-7.39 (d, 1H), 6.79-7.12 (m, 6H), 6.02 (s, 2H), 4.70-4.72 (d, 2H), 3.76-3.80 (d, 6H); MS m/z: 448(M+1).



66

{3-[5-(Benzo[1,3]dioxol-5-ylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-benzo[1,3]dioxol-5-ylmethyl-amine (Compound 66):

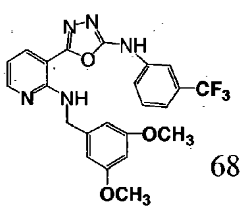
^{1}HNMR (DMSO-d6) δ 10.62 (s, 1H), 8.23-8.25 (m, 1H), 8.09 (t, 1H), 7.84-7.88 (m, 1H), 7.27-7.28 (d, 1H), 6.75-7.03 (m, 6H), 5.99-6.00 (d, 2H), 4.66-4.68 (d, 2H); MS m/z: 432(M+1).



67

(3,5-Dimethoxy-benzyl)-{3-[5-(4-trifluoromethoxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 67):

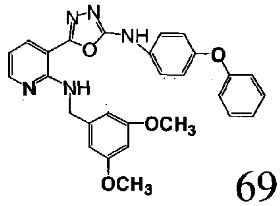
^{1}HNMR (DMSO-d6) δ 11.03 (s, 1H), 8.24-8.26 (m, 1H), 8.13-8.17 (t, 1H), 7.90-7.93 (m, 1H), 7.70-7.73 (d, 2H), 7.78-7.40 (d, 2H), 6.78-6.82 (m, 1H), 6.40-6.54 (d, 2H), 6.54-6.55 (d, 1H), 6.40 (s, 1H), 4.71-4.73 (d, 2H), 3.72 (s, 6H); MS m/z: 488(M+1).



68

(3,5-Dimethoxy-benzyl)-{3-[5-(3-trifluoromethyl-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 68):

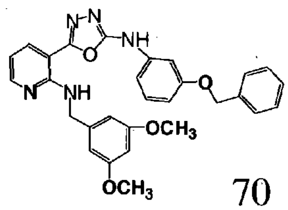
^{1}HNMR (DMSO-d6) δ11.20 (s, 1H), 8.11-8.27 (m, 3H), 7.90-7.93 (m, 1H), 7.79-7.82 (d, 1H), 7.58-7.64 (t, 1H), 7.37-7.39 (d, 1H), 6.77-6.82 (m, 1H), 6.40-6.54 (d, 2H), 6.39-6.40 (d, 1H), 4.71-4.73 (d, 2H), 3.72 (s, 6H); MS m/z: 472(M+1).



69

(3,5-Dimethoxy-benzyl)-{3-[5-(4-phenoxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 69):

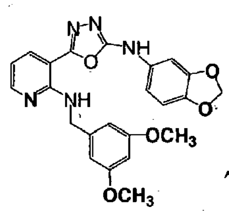
[1]HNMR (DMSO-d6) δ 10.80 (s, 1H), 8.14-8.25 (m, 2H), 7.90-7.93 (m, 1H), 7.62-7.90 (m, 2H), 6.77-7.40 (m, 7H), 6.54-6.55 (d, 2H), 6.39-6.40 (t, 2H), 4,78-4.80 (d, 2H), 3.71 (s, 6H); MS m/z: 496(M+1).



70

{3-[5-(3-Benzyloxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-(3,5-dimethoxy-benzyl)-amine (Compound 70):

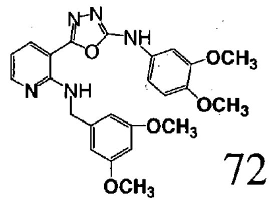
[1]HNMR (DMSO-d6) δ 10.81(s, 1H), 8.25-8.30 (m, 1H), 8.09-8.12 (t, 1H), 7.85-7.90 (m, 1H), 7.12-7.50 (m, 8H), 6.75-6.85 (m, 1H), 6.65-6.70 (m, 1H), 6.52-6.54 (d, 2H), 6.35-6.37 (t, 1H), 5.09-5.11 (s, 1H), 4.72-4.74 (d, 2H), 3.70 (s, 6H); MS m/z: 510(M+1).



71

{3-[5-(Benzo[1,3]dioxol-5-ylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-(3,5-dimethoxy-benzyl)-amine (Compound 71):

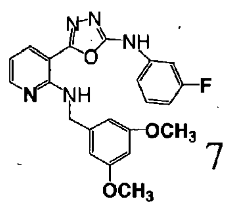
[1]HNMR (DMSO-d6) δ 10.64 (s, 1H), 8.12-8.24 (m, 2H), 7.86-7.89 (m, 1H), 7.28-7.29 (d, 1H), 6.76-7.04 (m, 3H), 6.54-6.55 (d, 2H), 6.39-6.41 (t, 1H), 6.00 (s, 2H), 4.70-4.72 (d, 2H), 3.72 (s, 6H); MS m/z: 448(M+1).



72

(3,5-Dimethoxy-benzyl)-{3-[5-(3,4-dimethoxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 72):

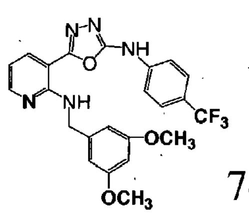
^{1}HNMR (DMSO-d6) δ 10.57 (s, 1H), 8.15-8.24 (m, 2H), 7.87-7,90 (m, 1H), 7.35-7,36 (m, 1H), 7.06-7.10 (m, 1H), 6.94-6.97 (d, 1H), 6.76-6.81 (m, 1H), 6.54-6.55 (d, 2H), 6.39-6.40 (t, 1H), 4.71-4.73 (d, 2H), 3.72-3.77 (m, 12H); MS m/z: 464 (M+1).



73

(3,5-Dimethoxy-benzyl)-{3-[5-(3-fluoro-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 73):

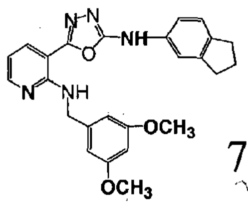
^{1}HNMR (DMSO-d6) δ 11.05 (s, 1H), 8.14-8.26 (m, 2H), 7.89-7.92 (d, 1H), 7.37-7.57 (m, 3H), 7.07-7.10 (d, 1H), 6.80-6.88 (m, 2H), 6.54 (s, 2H), 6.40 (s, 1H), 3.72 (s, 6H); MS m/z: 422 (M+1).



74

(3,5-Dimethoxy-benzyl)-{3-[5-(4-trifluoromethyl-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 74):

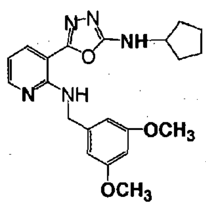
^{1}HNMR (DMSO-d6) δ 11.25 (s, 1H), 8.13-8.27 (m, 2H), 7.72-7.94 (m, 5H), 6.80-6.82 (m, 1H), 6.54-6.55 (d, 2H), 6.40-6.41 (t, 1H), 4.71-4.73 (d, 2H), 3.72 (s, 6H); MS m/z: 472 (M+1).



75

(3,5-Dimethoxy-benzyl)-{3-[5-(indan-5-ylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 75):

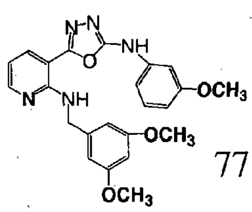
^{1}HNMR (DMSO-d6) δ 10.62 (s, 1H), 8.14-8.25 (m, 2H), 7.87-7.90 (m, 1H), 7.52 (s, 1H), 7.06-7.35 (m, 2H), 6.76-6.80 (m, 1H), 6.54-6.55 (d, 2H), 6.40 (s, 1H), 4.70-4.72 (d, 2H), 3.72 (s, 6H), 2.78-2.88 (m, 4H), 1.96-2.06 (m, 2H); MS m/z: 444 (M+1).



76

[3-(5-Cyclopentylamino-[1,3,4]oxadiazol-2-yl)-pyridin-2-yl]-(3,5-dimethoxy-benzyl)-amine (Compound 76):

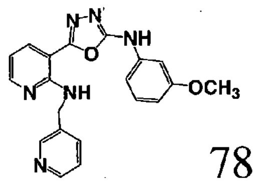
^{1}HNMR (DMSO-d6) δ 7.80-8.19 (m, 4H), 6.72-6.76 (m, 1H), 6.51-6.52 (d, 2H), 6.40 (s, 1H), 5.56-5.59 (d, 2H), 3.71 (s, 6H), 1.55-1.93 (m, 9H); MS m/z: 396(M+1).



77

(3,5-Dimethoxy-benzyl)-{3-[5-(3-methoxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 77):

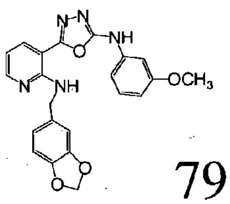
^{1}HNMR (DMSO-d6) δ 10.29 (s, 1H), 8.23-8.25 (m, 1H), 8.14-8.18 (t, 1H), 7.88-7.91 (m, 1H), 7.07-7.33 (m, 3H), 6.77-6.81 (m, 1H), 6.54-6.62 (m, 3H), 6.39 (s, 1H), 4.71-4.73 (d, 2H), 3.71-3.76 (d, 9H); MS m/z: 434(M+1).



78

{3-[5-(3-Methoxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-pyridin-3-ylmethyl-amine (Compound 78):

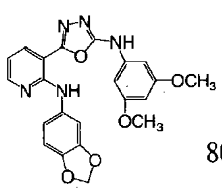
[1]HNMR (DMSO-d6) δ 8.61 (s, 1H), 8.45-8.46 (d, 1H), 8.22-8.30 (m, 2H), 7.89-7.91 (m, 1H), 7.76-7.79 (m, 1H), 7.13-7.36 (m, 4H), 6.72-6.83 (m, 1H), 6.59-6.61 (m, 1H), 4.82-4.84 (d. 2H), 3.76 (s. 3H); MS m/z: 375(M+1).



79

Benzo[1,3]dioxol-5-ylmethyl-{3-[5-(3-methoxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 79):

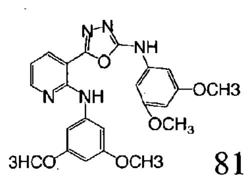
[1]HNMR (DMSO-d6) δ 10.60 (s, 1H), 8.10-8.15 (m, 1H), 7.88-7.92 (t, 1H), 7.61-7.70 (m, 1H), 6.41-7.14 (m, 8H), 5.85 (s, 2H), 4.49-4.51 (d, 2H), 3.62 (s, 3H); MS m/z: 418(M+1).



80

Benzo[1,3]dioxol-5-yl-{3-[5-(3,5-dimethoxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 80):

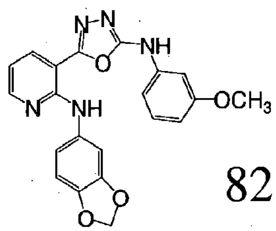
[1]HNMR (DMSO-d6) δ 10.95 (s, 1H), 9.94 (s, 1H), 8.42-8.44 (m, 1H), 8.06-8.11 (m, 1H), 7.62-7.63 (d, 1H), 6.91-7.14 (m, 5H), 6.31-6.33 (t, 1H), 6.12 (s, 2H), 3.86 (s, 6H); MS m/z: 434 (M+1).



81

(3,5-Dimethoxy-phenyl)-{3-[5-(3,5-dimethoxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 81):

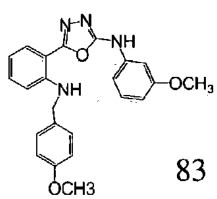
^{1}HNMR (DMSO-d6) δ 11.00 (s, 1H), 10.10 (s, 1H), 8.53-8.55 (m, 1H), 8.15-8.18 (m, 1H), 7.15-7.17 (m, 3H), 7.01 (s, 1H), 6.31-6.38 (m, 2H), 3.91-3.97 (m, 12H); MS m/z: 450 (M+1).



82

Benzo[1,3]dioxol-5-yl-{3-[5-(3-methoxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 82):

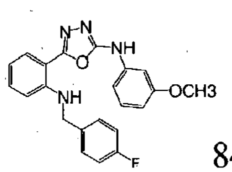
^{1}HNMR (DMSO-d6) δ 10.90 (s, 1H), 9.91 (s, 1H), 8.38-8.42 (m, 1H), 7.98-8.02 (m, 1H), 7.57-7.70 (m, 1H), 6.94-7.38 (m, 6H), 6.66-6.70 (m, 1H), 6.03 (s, 2H), 3.83 (s, 3H); MS m/z: 404 (M+1).



83

{5-[2-(4-Methoxy-benzylamino)-phenyl]-[1,3,4]oxadiazol-2-yl}-(3-methoxy-phenyl)-amine (Compound 83):

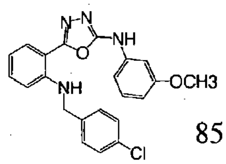
^{1}HNMR (DMSO-d6) δ 10.69 (s, 1H), 7.75 (s, 1H), 7.60-7.62 (d, 1H), 7.23-7.32 (m, 5H), 7.11-7.13 (d, 1H), 6.92-6.95 (d, 2H), 6.82-6.85 (d, 1H), 6.71-6.76 (t, 1H), 6.58-6.61 (d, 1H), 4.46-4.48 (d, 2H), 3.74-3.76 (d, 6H); MS m/z: 403 (M+1).



84

{5-[2-(4-Fluoro-benzylamino)-phenyl]-[1,3,4]oxadiazol-2-yl}-(3-methoxy-phenyl)-amine (Compound 84):

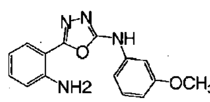
[1]HNMR (DMSO-d6) δ 10.71 (s, 1H), 7.82-7.88 (t, 1H), 7.60-7.65 (m, 1H), 7.10-7.46 (m, 8H), 6.70-6.85 (m, 2H), 6.55-6.62 (m, 1H), 5.54-4.58 (m, 2H), 3.78 (s, 3H); MS m/z: 391 (M+1).



85

{5-[2-(4-Chloro-benzylamino)-phenyl]-[1,3,4]oxadiazol-2-yl}-(3-methoxy-phenyl)-amine (Compound 85):

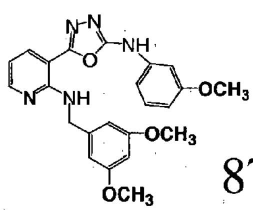
[1]HNMR (DMSO-d6) δ 7.91-7.94 (t, 1H), 7.60-7.62 (d, 1H), 7.10-7.41 (m, 8H), 6,67-6.77 (m, 2H), 6.55-6.58 (m, 1H), 4.57-4.59 (m, 1H), 4,57-4.59 (d, 2H), 3.76 (s, 3H); MS m/z: 407 (M+1).



86

[5-(2-Amino-phenyl)-[1,3,4]oxadiazol-2-yl]-(3-methoxy-phenyl)-amine (Compound 86):

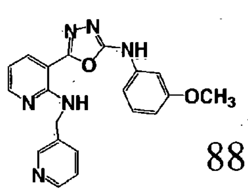
[1]HNMR (DMSO-d6) δ 10.63 (s, 1H), 7.54-7.55 (d, 1H), 7.12-7.52 (m, 4H), 6.87-6.90 (d, 1H), 6.59-6.70 (m, 4H), 3.77 (s, 3H); MS m/z: 283 (M+1).



87

(3,5-Dimethoxy-benzyl)-{3-[5-(3-methoxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 87):

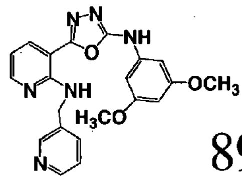
[1]HNMR (DMSO-d6) δ 10.30 (s, 1H), 8.23-8.25 (m, 1H), 8.14-8.18 (t, 1H), 7.07-7.33 (m, 3H), 6.62-6.81 (m, 1H), 6.40-6.59 (m, 3H), 6.39-6.40 (t, 1H), 4.71-4.73 (m, 2H), 3.67-3.76 (m, 9H); MS m/z: 434 (M+1).



88

{3-[5-(3-Methoxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-pyridin-3-ylmethyl-amine (Compound 88):

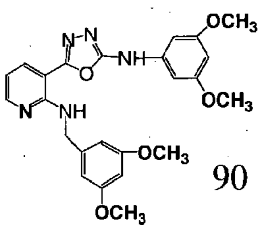
^{1}HNMR (DMSO-d6) δ 8.61 (s, 1H), 8.45-8.46 (d, 1H), 8.23-8.30 (m, 2H), 7.89-7.91 (m, 1H), 7.76-7.79 (m, 1H), 7.13-7.34 (m, 4H), 6.78-6.82 (m, 1H), 6.59-6.61 (d, 1H), 4.82-4.84 (d, 2H), 3.76 (s, 3H); MS m/z: 375 (M+1).



89

{3-[5-(3,5-Dimethoxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-pyridin-3-ylmethyl-amine (Compound 89):

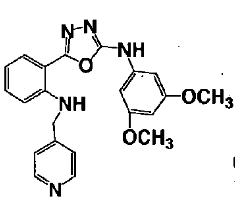
^{1}HNMR (DMSO-d6) δ 8.62 (s, 1H), 8.42-8.45 (t, 1H), 88.10-8.23 (m, 2H), 7.76-7.79 (d, 1H), 7.60-7.62 (m, 1H), 7.23-7.37 (m, 2H), 6.78-6.87 (m, 3H), 6.12-6.18 (m, 1H), 4.82-4.84 (d, 2H), 3.78 (s, 6H); MS m/z: 405 (M+1).



90

(3,5-Dimethoxy-benzyl)-{3-[5-(3,5-dimethoxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 90):

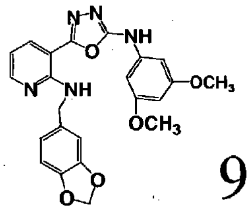
^{1}HNMR (DMSO-d6) δ 10.76 (s, 1H), 8.22-8.25 (m, 1H), 8.13-8.17 (t, 1H), 7.87-7.90 (m, 1H), 7.35-7.36 (d, 1H), 7.06-7.09 (m, 1H), 6.94-6.97 (m, 1H), 6.76-6.80 (m, 1H), 6.53-6.54 (d, 2H), 6.38-6.40 (t, 1H), 4.71-4.73 (d, 2H), 3.71-3.73 (m, 12H); MS m/z: 464 (M+1).



91

(3,5-Dimethoxy-phenyl)-(5-{2-[(pyridin-4-ylmethyl)-amino]-phenyl}-[1,3,4]oxadiazol-2-yl)-amine (Compound 91):

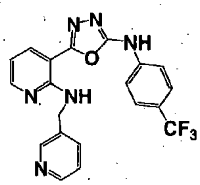
[1]HNMR (DMSO-d6) δ 8.24-8.26 (m, 1H), 8.08-8.12 (t, 1H), 7.86-7.89 (m, 1H), 6.77-7.00 (m, 6H), 6.19-6.20 (t, 1H), 6.00 (s, 2H), 4.67-4.69 (d, 2H), 3.74 (s, 6H); MS m/z: 404 (M+1).



92

Benzo[1,3]dioxol-5-ylmethyl-{3-[5-(3,5-dimethoxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 92):

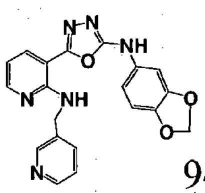
[1]HNMR (DMSO-d6) δ 10.60 (s, 1H), 8.51-8.53 (d, 2H), 8.00-8.01 (t, 1H), 7.62-7.64 (d, 1H), 7.24-7.37 (m, 3H), 6.88-6.89 (d, 2H), 6.68-6.78 (m, 2H), 6.20 (s, 1H), 4.66-4.68 (d, 2H), 3.76 (s, 6H); MS m/z: 448 (M+1).



93

Pyridin-3-ylmethyl-{3-[5-(4-trifluoromethyl-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-amine (Compound 93):

[1]HNMR (DMSO-d6) δ 8.62 (s, 1H), 8.46-8.47 (d, 1H), 8.23-8.29 (m, 2H), 7.68-7.92 (m, 6H), 7.34-7.38 (t, 1H), 6.78-6.82 (t, 1H), 4.82-4.84 (d, 2H); MS m/z: 413 (M+1).

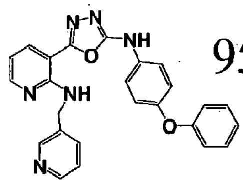


94

{3-[5-(Benzo[1,3]dioxol-5-ylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-pyridin-3-ylmethyl-amine (Compound 94):

[1]HNMR (DMSO-d6) δ 10.69 (br, s, 1H), 8.61-8.62 (d, 1H), 8.45-8.47 (m, 1H), 8.21-8.28 (m, 2H), 7.86-7.89 (m, 1H), 7.76-7.79 (d, 1H), 7.31-7.38 (m, 2H), 7.02-7.06

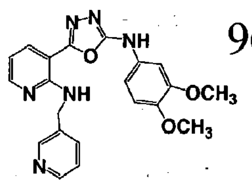
(m, 1H), 6.89-6.92 (m, 1H), 6.77-6.81 (m, 1H), 6.00 (s, 2H), 4.81-4.83 (d, 2H); MS m/z: 389 (M+1).



95

{3-[5-(4-Phenoxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-pyridin-3-ylmethyl-amine (Compound 95):

^{1}HNMR (DMSO-d6) δ 8.61 (s, 1H), 8.45-8.47 (m, 1H), 8.21-8.30 (m, 2H), 7.90-7.92 (m, 1H), 7.76-7.79 (m, 1H), 7.63-7.67 (m, 2H), 7.33-7.40 (m, 3H), 6.96-7.12 (m, 4H), 6.78-6.82 (m, 1H), 4.81-4.83 (d, 2H); MS m/z: 437 (M+1).



96

{3-[5-(3,4-Dimethoxy-phenylamino)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-pyridin-3-ylmethyl-amine (Compound 96):

^{1}HNMR (DMSO-d6) δ 8.62 (s, 1H), 8.44-8.46 (m, 1H), 8.21-8.31 (m, 2H), 7.76-7.90 (m, 2H), 7.32-7.40 (m, 2H), 7.06-7.10 (m, 1H), 6.93-6.96 (m, 1H), 6.77-6.93 (m, 1H), 4.81-4.83 (d, 2H), 3.67-3.77 (m, 6H); MS m/z: 405 (M+1).

Example 3: Compounds demonstrate anticancer activity (*In Vitro*)

The in vitro activity of the compounds was determined by the Sulphorhodamine B assay. (Skehan P, Storeng R, Scudiero D, Monks A, McMahon J, Vistica D, Warren JT, Bokesch H, Kenney S, Boyd MR. New colorimetric cytotoxicity assay for anticancer-drug screening. *J Natl Cancer Inst* 82, 1107-1112, 1990).

Sulphorhodamine B binds to basic amino acids and stains proteins which can be eluted and detected spectrophotometically by measuring absorbance at 515 nm. The absorbance is indicative of the total protein content of the cells fixed to the walls of the plate well at a given time by trichloroacetic acid, which is a measure of the viable cell concentration.

Reagents:

Sulphorhodamine B (Sigma Cat#S-1402)	0.4%(w/v) in 1%(v/v) acetic acid
Trichloroacetic acid (Sigma Cat#T-9159)	50% (w/v) in deionized water, working solution
Trizma base (Tris) (Sigma Cat#T-7693)	10mM working solution, pH 7.5

Procedure:

Day1:

Seed 10,000 cells/100uL/well in 96 well plate in duplicates as per template. Seed cells in extra plate for time zero (To plate).

Incubate cell for 24 hours at 37°C with 5% CO_2

Day2:

Add the test compound/drug to the cells at five log doses from 100uM to 0.01uM (Volume of addition=100 uL in 1% DMSO for all compound concentrations, Control treatment= 1% DMSO).

*Preparation of test compounds:

Weigh test compounds in 1.5mL eppendorf tubes. Calculate the volume of DMSO to be added to bring the concentration of the compound to 20 mM.

Make the 20 mM stock into four 10 fold dilutions in DMSO to get 2, 0.2, 0.02 and 0.002mM solutions. Dilute each solution 100 times (10uL to 1ml medium); further addition to the culture plate (100 uL) will half the concentration as cells are already in 100 uL medium. The final concentration in the wells for 20mM stock will be 100uM and similarly with other test concentrations.

Incubate cell for 48 hours at 37°C with 5% CO_2.

"To" plate is terminated by adding 50uL of 50% cold Trichloroacetic acid (10% to final). Incubate for one hour at 4^0C.

Day 4:

Cells are fixed to the wells by the addition of 50uL of 50% cold Trichloroacetic acid (10% to final) and incubating for 1 hour at 4°C.

The supernatant is discarded by force inverting the plate into the sink followed by washing thrice with tap water and the plates are then air-dried.

100 uL SRB (0.4 % in 1 % acetic acid) is added to each well and the plates are incubated for 10 minutes at room temperature. Unbound dye is removed by force inverting the plate into the sink and washing thrice with 1 % acetic acid. Allow the plates to air dry.

Bound SRB is solubilized with 100uLof 10mM Tris, pH 7.4 and the absorbance is measured at a wavelength of 515 nm.

Calculations:

Percentage growth is calculated by:

T-To/C-To X 100 if T > To

T-To/To X 100 if T < To

Where T - Test OD (with compound)

C – Control OD

To- Time Zero OD (Cell growth at the time of drug addition)

A plot with concentrations on X axis and percentage growth on Y axis is drawn and the intercepts at 50, 0 and -50 on the scale will give the GI50.

GI50 stands for the concentration of compound required to inhibit 50% tumor cell growth.

The in vitro activities of the compounds were determined in the following eleven human cancer cell lines. The representing GI50 values are listed in the following tables:

Table 1: *In vitro* anticancer activity against HT 29 cells

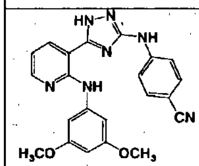
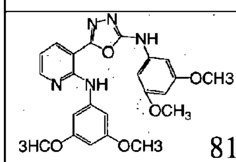
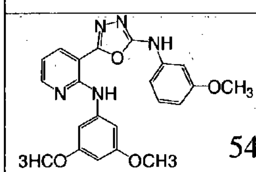
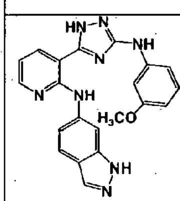
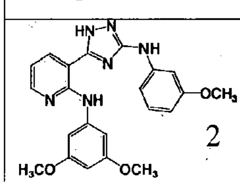
Compound	GI50 (uM)
 4	2
 81	2
 54	0.1
 23	2.2

Table 2: *In vitro* anticancer activity against A431

Compound	GI50 (uM)
 2	0.03

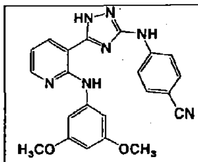
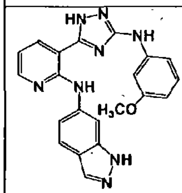
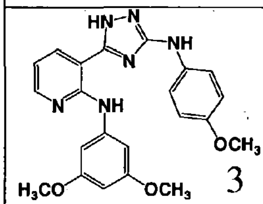
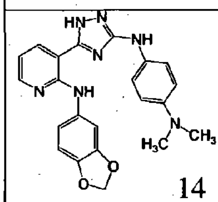
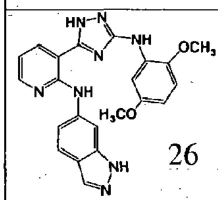
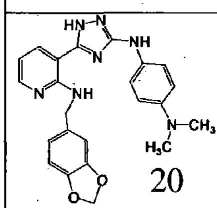
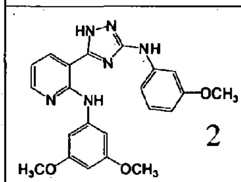
 4	2
 23	1.5
 3	1.75
 14	0.25
 26	1.5
 20	0.3

Table 3: *In vitro* anticancer activity against MCF7

Compound	GI50 (uM)
 2	1.5

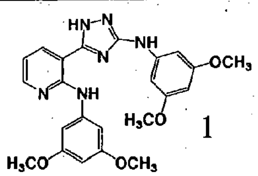
 1	0.4

Table 4: *In vitro* anticancer activity against HCT-8

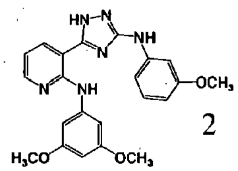
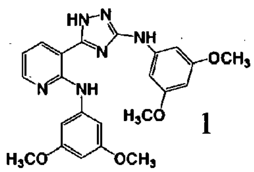
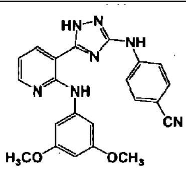
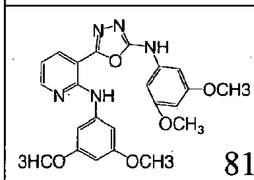
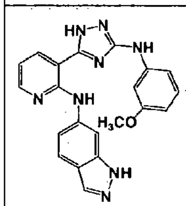
Compound	GI50 (uM)
 2	1.5
 1	0.4

Table 5: *In vitro* anticancer activity against HCT116

Compound	GI50 (uM)
 4	0.22
 81	0.15
 23	1.5

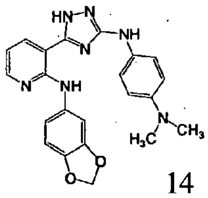
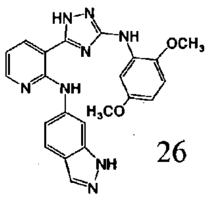
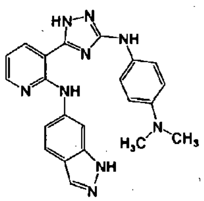
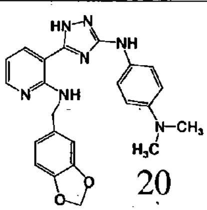
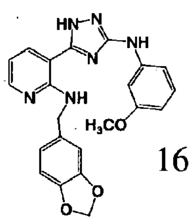
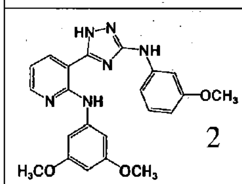
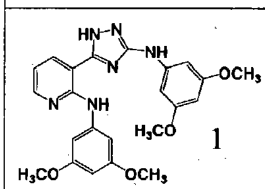
 14	0.04
 26	0.45
 27	0.15
 20	0.02
 16	0.4

Table 6: *In vitro* anticancer activity against DLD-1

Compound	GI50 (uM)
 2	0.07
 1	0.8

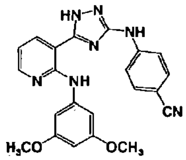
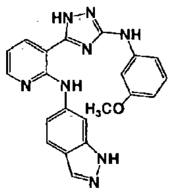
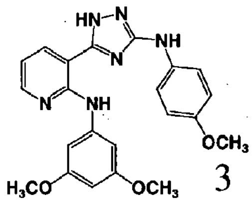
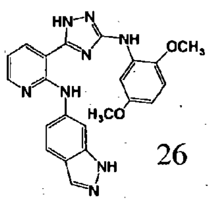
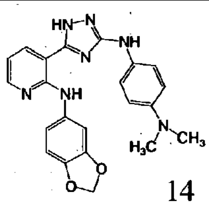
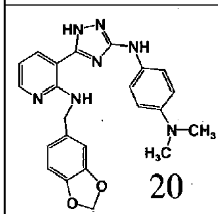
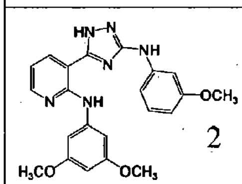
 4	0.5
 23	0.5
 3	1.5
 26	0.05
 14	0.09
 20	0.09

Table 7: *In vitro* anticancer activity against LoVo

Compound	GI50 (uM)
 2	0.02

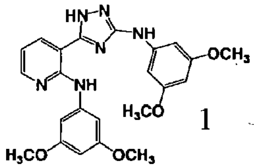
 1	0.1

Table 8: *In vitro* anticancer activity against SKOV3

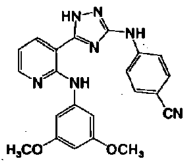
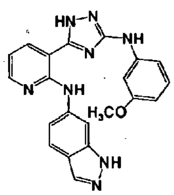
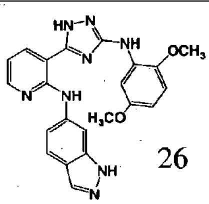
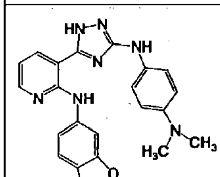
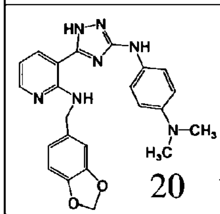
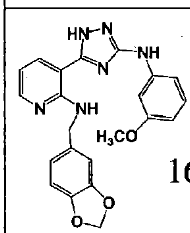
Compound	GI50 (uM)
 4	1.75
 23	0.1
 26	0.35
 14	0.04
 20	0.02
 16	0.8

Table 9: *In vitro* anticancer activity against PC3

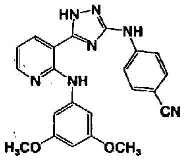
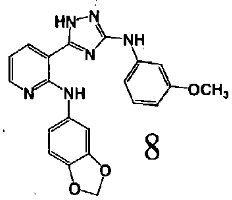
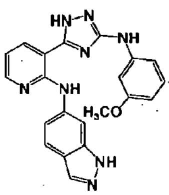
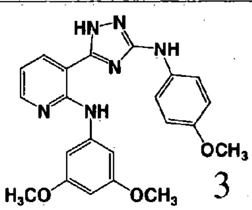
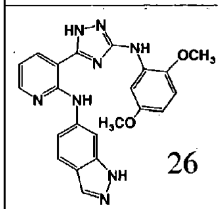
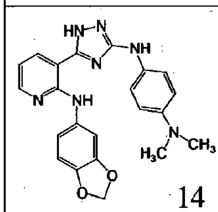
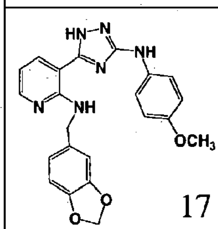
Compound	GI50 (uM)
 4	1
 8	2.2
 23	0.15
 3	1.5
 26	0.3
 14	1
 17	1.25

Table 10: *In vitro* anticancer activity against DU145

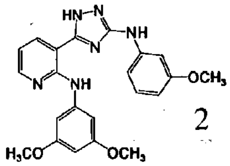
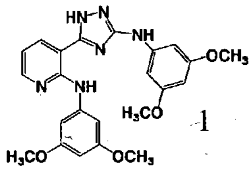
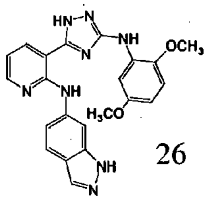
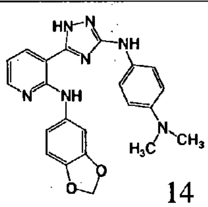
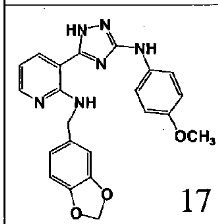
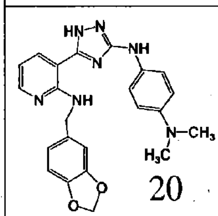
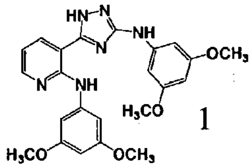
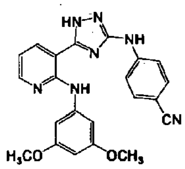
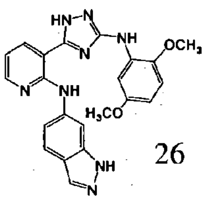
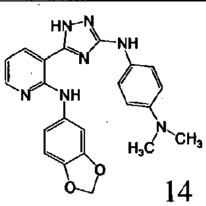
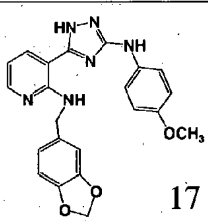
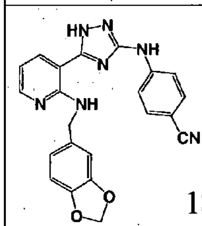
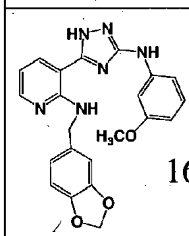
Compound	GI50 (uM)
 2	0.015
 1	0.01
 26	1
 14	0.3
 17	1.25
 20	0.35

Table 11: *In vitro* anticancer activity against GEO

Compound	GI50 (uM)
 1	0.01
 4	2.5
 26	1.75
 14	2
 17	1.25
 18	0.03
 16	0.15

The above examples are intended to be illustrative only. In particular, the invention is not intended to be limited to the methods, protocols, conditions and the like specifically recited herein, insofar as those skilled in the art would be able to substitute other conditions, methods, amounts, materials, etc. based on the present disclosure to arrive at compounds within the scope of this disclosure. While the present invention is described with respect to particular examples and preferred embodiments, the present invention is not limited to these examples and embodiments. In particular, the compounds of the present invention are not limited to the exemplary species' recited herein. Moreover, the methods of the present invention are not limited to treating only the exemplified diseases and conditions, but rather any disease or condition that may be treated by regulation of kinases. Additionally, the methods of synthesis of the present invention are not limited to the methods exemplified in the example. The methods of the present invention include methods of making any of the compounds set forth in the present invention that those skilled would be able to make in view of the present disclosure, and are not limited to the exemplified method. For example, methods encompassed by the present invention may involve the use of a different starting material depending on the desired final compound, different amounts of various ingredients, or substitution of different ingredients such as other reactants or catalysts that would be suitable depending on the starting material and result to be achieved.

ABSTRACT

The present invention relates to heterocyclic compounds that have anticancer activity, and pharmaceutical compositions that contain such compounds, methods of treating diseases and conditions in mammals using such compounds and composition and methods for their manufacture.